observation poses questions of the qualitative action of procaine in addition to questions of the quantitative action.)

Thus, although Yau (33) found that certain monoamine oxidase preparations are more sensitive to procaine, only marginal effects could be detected in vivo after intraperitoneal administration to mice of massive doses of 60 mg/kg or more. This dose is a huge one on the basis of any kind of extrapolation to man. Moreover, the relationship clinically between antidepressant properties and inhibition of MAO remains a point of some contention; it may well be that clinical antidepressive activity is not directly the consequence of MAO inhibition.

A review of these data leads to the hypothesis that if the claim can be verified that procaine solutions have demonstrable effects in man when administered intramuscularly in daily doses of 10 ml of a 2 percent solution, then the actions are probably the consequence only of the local effects of the injections since the maximal systemic levels of procaine (or PABA or DEAE) achieved would be insufficient to alter neural or enzyme activities.

The claim that Gerovital is specially stabilized in order to increase the biologic half-life of the active ingredient, procaine hydrochloride, has not been substantiated. Although the possibility remains that procaine would reach unusually sensitive brain cells or sites in adequate concentrations, data to support the idea are lacking. It is also possible to postulate a monoamine oxidase unusually sensitive to the inhibitory effects of procaine. That various types of monoamine oxidases are present in brain is now well-established (34). Although one can argue that procaine could act in minute concentrations on specially located and sensitive monoamine oxidases, there is no evidence that this is so.

The frequent claims of the clinical literature that procaine preparations are not detectable by the subjects and that they are without any side-effects are puzzling. Reactions to procaine injected into muscles, joint spaces, or along nerves have long been known to have a number of effects including:

a) numbness at the site of injection (hence its use as a local anesthetic — the 2 percent present in Gerovital is a standard local anesthetic concentration).

b) hypotension or peripheral vasodilation if absorption is especially rapid; and

c) local or systemic allergic reactions in sensitive individuals.

PROCAINE AND GEROVITAL H-3

A wide variety of claims have been made from time to time by various investigators employing Gerovital H-3, both with respect to its composition and to its effects. At present, the claims emphasize that Gerovital H-3 action is due to procaine [for example, Aslan (35)].

The common procedures for verification of the composition of pharmaceutical preparations have not been employed for Gerovital. There is one reference in the literature of an analysis of a single sample of Gerovital [Gordon et al (36)]. This single report of a single sample has been frequently cited as indicating the composition of all Gerovital preparations [for example, MacFarlane and Besbris (31)]. The data obtained by Gordon et al (36), interestingly, do not agree with those provided in the trade literature [Jarvik and Milne (37)] for the composition of Gerovital H-3.

Thus, there exist little if any other analytic or quality control data on samples of Gerovital H-3. In fact, this reviewer suggests that the composition is not consistent; it undergoes at least the variation in procaine concentration due to spontaneous hydrolysis.

In the absence of data to the contrary, it must also be entertained that the commercial preparations may contain other substances or other active ingredients. These questions could be readily resolved by the use of the well established routine techniques for even minimal quality control of pharmaceutical preparations.

The question of the possibility of unique characteristics of Gerovital or GH-3 over procaine has been addressed explicitly by Cherkin (38), Jarvik and Milne (37) and Morin and Cummins (39). With respect to the specific claims, Aslan has reemphasized, as have so many previous authors, that the Gerovital preparation is "specially stabilized" or is "buffer stabilized" so as to provide a "longer half-life of the whole molecule of procaine." Further, the claim is made that use of the low pH of 3.3 reduces the rate of hydrolysis. To date there is no evidence that the procaine of Gerovital is any longer lasting in vivo when administered according to the Aslan techniques than is any other of the commercially available solutions of procaine hydrochloride. This has been experimentally verified by Morin and Cummins (39). Moreover, there is little reason to expect any difference among procaine preparations since the procaine is absorbed into the blood stream, and the blood and body tissues form a vast reservoir relative to the amount of procaine.

Procaine is rapidly split by the action of plasma cholinesterase (30).

The argument regarding the special stability might have some merit if it referred to only the local destruction of procaine, although there is some question of its relevance in view of the extensive buffering capacity of most body tissues.

It is claimed that the benzoic acid added to the preparation forms a complex with procaine which in some way protects it from destruction. This claim also lacks any experimental verification, and such evidence would be easy to generate. It further lacks rationality since such complexes are admittedly weak and readily reversible in plasma or extracellular fluid.

The claim that Gerovital has a uniquely low acid pH as compared with other procaine preparations is erroneous and misleading inasmuch as most manufactured procaine solutions are acid, with a pH not appreciably different from the 3.3 or 3.68 stated for Gerovital [cf. Cherkin (38)].

Thus, the claims for special stabilization, prolongation of half-life, special formulation, buffered stabilization, and less alkalinity than other comparison solutions of procaine [e.g., Zung et al (40) stated that "the usual pH of the commercially available procaine solution varies between 5.5 to 7.6,"] are all false, misleading, or fraudulent. (Claims relating to efficacy due to the metabolic products would also detract from the assertion that the parent substance produces in vivo inhibition of monoamine oxidase as a mechanism of action. If one claims enough different things, it is possible that one of them might turn out to be correct.)

This general criticism is not meant in any way to confirm or deny the presence of potential changes in the clinical status of patients receiving Gerovital. Such claims are appropriately assessed on their own merit!

Taken together, all of the various claims for special pharmacologic qualities of GH-3 are applicable only in increasing its potency or duration of action *at the site of its administration* intramuscularly. Further, such increased stability, if it occurs, would tend to retard the systemic absorption of procaine solution and thus decrease the maximum levels obtainable in such sites as the brain.

The second major issue centers on the possible actions of the metabolic products of procaine, para-aminobenzoic acid (PABA) and diethylaminoethanol (DEAE). With respect to PABA, the levels obtainable are so low as to have minor significance in terms of dietary or other sources of this acid. Moreover, if PABA is the active ingredient, then a far more rational approach to therapy would be its direct administration rather than via the complicated administration of procaine.

With respect to DEAE, this substance has a longer half-life in man than procaine or PABA (30). One can speculate that high levels of DEAE could have pharmacologic effects. However, this is doubtful even though deanol, the dimethylaminoethanol analog, does appear to have some demonstrable clinical effects, at least in tardive dyskinesia (41–43). Pfeiffer et al (44) have long claimed that the latter agent has stimulant effects [see also Ostrow (45) and Connors (46)].

The question of the efficacy of deanol, a congener of DEAE, remains seriously disputed and there are few relevant data on DEAE. What few tests have been carried out have been negative [for example, Verzar (47)].

It should be recognized that the possibility of the metabolic products being active would constitute a direct negation of all the claims of the efficacy of this specially "stabilized" procaine solution, since any procaine solution would give rise to the same metabolic products and should, therefore, exhibit the same therapeutic efficacy.

To summarize: there are absolutely no data relating to the quality control of the composition of Gerovital preparations or of the additives. The absence of such readily obtainable, inexpensive, standard analyses — analyses expected and required by custom and law for all other pharmaceutical and food preparations — greatly restricts the capacity to evaluate and understand the effects of Gerovital.

SUMMARY OF PHARMACOLOGIC CHARACTERISTICS OF PROCAINE

1. Procaine hydrochloride exerts effects on most neural systems and excitable cells in concentrations of 2–20 mg/ml. These effects include: a) a decrease in membrane excitability, b) an increase in threshold, c) slowing or blocking of action potential conduction, d) decrease or loss of repetitive activity such as cardiac arrthymias or sensory nerve discharge, and e) reduced efficacy of synaptic transmission, usually without alteration in resting membrane potential.

2. All neural effects of procaine appear related to changes in membrane ionic conductances involving sodium, potassium, or calcium.

3. Procaine is readily absorbed, distributed and metabolized following intramuscular administration.

4. The actions of procaine on brain and spinal cord are transient and require intravenous doses of over 2 mg/kg in experimental animals.

5. If intramuscular doses of 10 ml of 2 percent procaine solution are eventually proved to have clinical effects in man, then these effects are probably indirect consequences of the local effects of the injection; procaine levels at other than the site of injection are simply insufficient to alter neural or enzyme activities.

6. It has not been proved that Gerovital is especially stabilized, or acts better or differently than other solutions of procaine.

PROCAINE AS A MOOD ELEVATOR

In her original report (35b) Aslan claimed phenomenal improvement in the psychic functioning of 109 elderly subjects who had undergone procaine therapy. Some disoriented psychiatric patients recovered. Memory, concentration, and perception were improved as well as depression.

She noted that many of the procaine preparations used by others were not the same as the Roumanian product, Gerovital. She stated that Gerovital differed from most procaine preparations in its pH and in its content of benzoic acid, potassium metabisulfite, and disodium phosphate. She noted that many clinicians had not followed her suggested dosage regimen and had not continued the therapy long enough to achieve therapeutic effects.

Bucci and Saunders (48) studied 25 chronically psychotic women between the ages of 40 and 80 who had been hospitalized for periods ranging from 2 to 24 years and had failed to respond to phenothiazine drugs. The patients were given procaine hydrochloride three times per week in doses of 100 mg, for six months. Then they were given 160 mg three times per week for the next three months. The evaluations were based on changes during the nine months of treatment. In 3 cases the drug was discontinued because of weight loss and mental deterioration. The results showed alleviation of depression as well as decrease of psychotic symptoms associated with schizophrenia. There was improvement in both the physical and mental status of the patients. Two patients were discharged from the hospital. Seven manifested moderate improvement, 6 slight improvement, 6 no improvement, and 3 became worse. No control group was used.

Kral et al (49) studied 32 hospitalized patients (average age, 81.1 years) with senile and arteriosclerotic psychoses, as well as 20 outpatients (average age, 72) who were being treated for functional or organic psychiatric disorders. Among the inpatients, 11 received 2 percent procaine hydrochloride for 13 months, 11 received it for six months, and 10 received physiologic saline. Procaine in neither group appreciably altered the symptoms and course of the basic senile or arteriosclerotic brain disease. A temporary improvement in depression was noted, as was an increased level of activity. The improvements were not sustained. The outpatients with functional disorders responded equally well to saline and procaine. The three groups were not differentially affected by procaine and saline. In all three groups, behavior became worse as measured by seven items relating to physical condition, memory, mental symptoms, incontinence, appearance, activity and social contact. All showed decreased performance on a memory scale.

May et al (50) studied 107 aged female patients in a double-blind trial. The experimental group received 2 percent procaine HCl at a pH of 3.5–4.0. The patients were evaluated four times: 4–5 months before treatment, 1 month before, 6 months after the start of treatment, and 1 year after the start of treatment. No significant differences for age, length of hospitalization, and memory quotient were demonstrated between the procaine and saline groups. Altogether, 51 of 54 patients in the experimental group and 49 of 53 in the control group completed the study. For memory quotient, no significant difference was found between the groups after treatment. Basically the study's findings were negative for differences between procaine and saline.

Smigel et al (51) studied 60 nursing home patients (ages 35 to 98) who had arthritis, nervous disorders and senile mental disturbances and who had received little or no benefit from other treatment. They were given 2 percent procaine buffered at a pH of 3.5. Later, 5 patients received Gerocaine, another procaine preparation. This double-blind study of 60 patients was coded by a procedure that can be inadequate. Odd-numbered patients received procaine and even-numbered patients received the control substances. Such a code is easily broken. During the course of the study, unaffected controls were taken out of the trial to see if they would improve with procaine therapy, and vice versa. Of the 29 patients receiving procaine, 25 showed improvement in 5 months. Of the 21 controls (placebo injections), 9 showed improvement. Nine controls and one ex-

perimental subject terminated their participation prematurely. Positive results were found mainly for patients with chronic nervous disorders, but not for those with chronic brain syndrome. The conclusion drawn by the authors was that procaine exerted markedly beneficial effects in the experimental group.

Lewicki et al (52), a group of clinical psychologists in Poland, evaluated the responses of elderly patients to long-term treatment with Gerovital. They assessed memory, thoughts, and associations. Seventy-five percent improved but 25 percent were no better. Improvement was not solely attributable to Gerovital because other measures to improve health were used.

In 1971, Cohen and Ditman (53) reported findings on 41 patients — 17 normal, 17 with psychiatric disorders, and 7 with major medical problems accompanied by depression with or without anxiety. These patients were given 100–200 mg of Gerovital three times per week over a four-week period. They were rated by psychiatric interview, mood scale, and a modified Zung scale of depression. They were well educated, knew of the benefits claimed for Gerovital, and volunteered in the hope that it would relieve their symptoms. Of the 41 patients, 35 reported improvement in one or more of the areas evaluated, e.g., well-being, relaxation, energy, libido, motivation, and somatic discomfort. This was an open study with a highly selected group of patients. Because of placebo effects, the patients were likely to respond positively.

Sakalis et al (54) studied 10 senile arteriosclerotic inpatients with depression of two or more years' duration. They were given Gerovital, 100–200 mg three times per week for three weeks. There were no side effects. The patients were given placebo for one week (baseline), active drug for three weeks, and then post-drug placebo for two weeks. No clinical change was noted till the end of the second week. By then, 6 out of 10 were receiving 200 mg per injection. They were rated weekly on the Hamilton Depression Scale, Clinical Global Impression (CGI) and the Nurse's Observation Scale for Inpatient Evaluation. Altogether six ratings were obtained. Statistically significant positive changes were obtained on the Hamilton Scale for somatization and anxious depression ($p < .05$). Symptoms increased during the first placebo week and then decreased during the second placebo week. The CGI showed no significant changes. No changes occurred for orientation, memory, paranoid ideation, and insight. There was a transient amelioration of depressive symptoms. The authors concluded that Gerovital had a mild and transient beneficial effect in high doses, but this was obscured by the variability of the clinical picture in demented patients.

Zung et al (40) recently published the results of a double-blind study comparing intramuscularly administered Gerovital with orally administered imipramine and with placebo given both intramuscularly and orally. The subjects were volunteers 60 years of age or older. The following measures were used: Clinical Global Rating of Depression (CGRD), Zung Self-rating Depression Scale (SDS), Self-rating Anxiety Scale (SAS), Depression Statue Inventory (DSI), and Anxiety Status Inventory (ASI). Ratings were obtained on day zero and day 28. Patients were drug-free for seven days prior to the 4-week treatment regimen of 5 ml of Gerovital administered three times for the first week and then 10 ml three times per week for the last three weeks — a total dose of approximately 2,100 mg of procaine. The imipramine group received 25 mg at bedtime for day one, 25 mg twice a day for day two, 25 mg three times a day for days three to fourteen, and 25 mg four times a day for weeks three and four.

Although the preparations and rates of administration were different, each patient received the preparations by both routes (Gerovital intramuscularly plus placebo orally, or imipramine plus placebo parenterally, intramuscularly or orally). Three patients of 36 dropped out. Nine completed the Gerovital regimen, 11 the imipramine regimen, and 10 the placebo regimen. The average dose of Gerovital was 2,022 mg (procaine), and of imipramine 74.8 mg. At day zero, there were some differences in test scores. The imipramine group was more symptomatic than either of the other two groups. The Gerovital group improved significantly on the CGRD, the DSI, SDS, ASI, and SAS. The imipramine group improved significantly on all measures except the SAS. The placebo group did not change significantly.

Comparison for differences on the CGRD revealed no difference between the imipramine and Gerovital group or the imipramine and placebo group, whereas the Gerovital group differed significantly from the placebo group. On the DSI, the imipramine group was more symptomatic than the Gerovital group but did not differ from the placebo group. The Gerovital and placebo groups did not differ significantly. At day 28, the Gerovital group scored lower than the imipra-

mine group. The Gerovital and placebo groups and the imipramine and placebo groups did not differ on day 28. For change score, no differences were found between the groups.

For SDS at day zero, the Gerovital group scored lower than the imipramine group. Imipramine versus placebo and Gerovital versus placebo scores did not differ. At day 28 the Gerovital group scored lower than the imipramine group. The other two group differences were still insignificant. For change score, the only significant difference was between the Gerovital and the placebo group.

On the ASI at day zero, no significant differenes were found. At day 28 the Gerovital group achieved a lower score than the imipramine group. According to the test, the imipramine group score was lower than that of the placebo group. This is an inconsistency, since the Gerovital and placebo groups did not appear to differ at 28 days. No significant difference was found for change scores.

For SAS at day zero, scores for the Gerovital group were lower than for the imipramine group and the placebo group. Imipramine versus placebo differences were not significant. At day 28 the differences persisted for Gerovital versus imipramine and Gerovital versus placebo. Placebo versus imipramine differences were not significant. All change score differences were not significant. Although the patients receiving active substances reported more dizziness and more confusion, no significant differences for side effects were demonstrated.

This study was better controlled than earlier ones on Gerovital, and compared the antidepressant effects of Gerovital with those of imipramine, a highly regarded tricyclic antidepressant drug. The statistical analysis reported for these studies was probably inadequate since the groups differed significantly at day zero. An analysis of covariance probably should have been used instead of a *t* test.

SUMMARY OF DATA ON PROCAINE AS A MOOD ELEVATOR

The most tenable conclusion to be drawn from the studies reviewed is that suggestive evidence of a transient antidepressant effect was obtained. Defects in the designs of the studies, statistical analysis, and instruments employed [except for the studies of Sakalis et al (54) and Zung et al (40)] make it impossible to state unequivocally that Gerovital is an effective antidepressant. More carefully controlled studies should be undertaken to determine definitively whether Gerovital is an effective antidepressant agent.

Monoamine oxidase inhibitors block the deamination of norepinephrine, thereby increasing the levels of norepinephrine available to receptors in an active form. However, it is not certain that this is the effect that inhibits depression or that all monoamine oxidase inhibitors have an antidepressant effect. Tricyclic agents, several of which are effective antidepressants, have no effect on monoamine oxidase, but work by interfering with the uptake of norepinephrine into adrenergic neurones, both central and peripheral (1).

PROCAINE IN SENILE DEMENTIA AND CEREBRAL ATHEROSCLEROSIS

A large number of publications have dealt with the relative effectiveness of procaine and Gerovital in senile dementia and cerebral atherosclerosis. Those studies without controls will be discussed first. Galindez (55) noted improvement in depression when procaine was combined with dehydroandrosterone. Bizzi and Albonetti (56) reported similar improvement when procaine was combined with multiple vitamins.

In a study by Pascal and Bezusso (57), 19 of 29 elderly patients showed slight improvement in senile psychosis; 11 of 29 felt better and had less anxiety; 4 of 29 slept better, and 3 of 20 hallucinated less frequently. Giore (58) reported that 7 of 10 elderly women treated with procaine improved on a vocabulary test and 8 of 10 did better on the Progressive Matrices Test.

Silbergleit (59) treated elderly asthenic and depressed patients with a combination of procaine, vitamins, and reserpine. He noted improvement in asthenia and depression as well as increased appetite, weight gain, euphoria and an optimistic attitude. Balganon (60) combined procaine with para-aminobenzoic acid and noted great improvement in about a third of a group of patients. Nearly half of the group improved moderately. Similar results were reported by Greppi (61), Paule (62), Student and Vlach (63), Aslan (64), Skula (65) and Letourmey (66). Oury and Delvaille (67) treated 1,000 inpatients and 16,200 outpatients and observed increased memory and attention span.

Not all the uncontrolled studies reported beneficial effects. Piro et al (68) treated 31 patients and concluded that procaine was of no help in neuropsychiatric deterioration due to aging. Scardigli and Guidi (69), and Scardigli (70) and

Giore (58) reached similar conclusions. Gericke et al (71) reported no benefit in a study of 39 patients. O'Connell and Offner (72) and Friedman (73) were unconvinced that procaine was beneficial in chronic brain syndrome.

Among the controlled studies, Kant and Sterne (74) carried out a double-blind trial of procaine versus sterile sodium chloride. There were 10 patients in each group and ages ranged from 60 to 93, with a mean of 76. The patients had various physical diseases and manifested intellectual deterioration. They received nine series of procaine injections over a year. Changes in both groups on physiologic indices over a year were recorded. No differences were found between the placebo and procaine groups for changes in physiologic measures, memory, and intellectual functions. Procaine was not more effective than saline.

Long and Gislason (75) studied 33 patients in a state mental hospital in a double-blind protocol for one year. Patients were disoriented for time and place. Seventeen received procaine, and 16 saline solution. There was a trend to increased orientation, attention, and memory in the group treated with procaine, whereas a decrease in orientation, attention, and memory were noted in the control group.

Berryman et al (76) conducted a double-blind study. The subjects were 40 women over age 50 who received four 12-week courses of treatment, with 24 injections of 100 mg of procaine per course. There was no evidence of benefit from procaine therapy.

Isaacs (77) carried out a double-blind crossover study, using patients as their own controls. Twenty-four patients with cerebral atherosclerosis participated. Ten psychologic characteristics were assessed on 3-point or 4-point scales. Two courses of injections of 10 weeks each were given. Ten patients prematurely stopped treatment. No significant changes for procaine were noted, and no significant differences were found between procaine and a control substance. With procaine, 3 of 14 patients improved in more than two characteristics; 6 of 14 deteriorated in more than two characteristics. With saline, 4 of 14 patients improved in more than two characteristics and 8 of 14 deteriorated in more than two characteristics. No significant effect of procaine was observed.

Hirsch (78), in a double-blind study, used procaine versus sterile water, 5 ml three times a week for four weeks. There were 34 subjects (18 controls and 16 receiving active substance). Premature termination occurred in 8 controls and in 1 procaine patient. No differences were found between the two groups for change in status. With the control substance, 1 subject deteriorated, 3 showed no change, 3 improved, and 2 showed marked improvement. With the active substance, none deteriorated, 7 showed no change, 3 improved, and 2 showed marked improvement.

Fee and Clark (79) conducted a double-blind study in which procaine hydrochloride and isotonic saline were compared in a group of hospitalized inpatients and a group of residents in welfare accommodations. The substances were given intramuscularly three times a week for nine trials of four weeks each. Mental status, mobility, and incontinence were rated. The hospitalized group consisted of 12 men and 12 women. All showed confusion and incontinence. After one year, 10 of the patients had died, 5 were worse, and 8 were stationary. The results showed no difference between placebo and procaine effects. The group living in welfare accommodations consisted of 20 men and 20 women. Half deteriorated or died. With the control substance, 9 died or were worse; with procaine, 10 died or were worse. Eight receiving the control substance and four receiving procaine remained unchanged. Three improved with the control substance, and 6 with procaine. Clinical ratings revealed that 4 improved with the control substance, and 2 with procaine. Seven receiving the control substance and 3 receiving procaine remained stationary. Nine receiving the control substance and 10 receiving procaine became worse. The patients' subjective reactions and the clinicians' ratings both showed no significant differences. Clearly, procaine was not beneficial.

Gitman et al (80) reported a study in which procaine (5 ml) three times a week was given for 12 injections, followed by 10 days of rest and a second series of 12 injections. Ten subjects were studied. One of the 10 showed significant improvement, mainly in dyspnea associated with asthma; 2 gained weight, and 1 lost weight. Only 2 of the 10 could be considered to have shown any clinical improvement.

In a study by Cashman and Lawes (81), the Wechsler Memory Scale, Bender-Gestalt, Raven's Progressive Matrices, and the Mills Hill Vocabulary Definition Scale were used to compare 6 control patients with 6 procaine patients. Five of the 6 control subjects improved; 4 of the 6 procaine patients deteriorated. The study was not double-blind, and other treatments were administered.

Abrams et al (82) reported a double-blind study

starting with 121 subjects, of whom 70 were recruited and 63 were volunteers. Of the 63 volunteers, 60 started and 40 finished. Eight died and 22 refused to continue or ended the trial prematurely. Twenty-two received "European" procaine (Gerovital) and 18 received "American" procaine. Pre- and post-study evaluations involved ratings of the face-hand test, degree of brain impairment, degree of disorientation in time and space, memory defect, affect depression, delusions, capacity to articulate through speech, capacity for interpersonal relations, and extent of ego and intellectual impairment; these ratings were made by psychiatrists. Psychologists rated psychologic integration, energy, physical appearance, memory, and state of mind. Nurses and family members also rated patients. Only positive changes were considered. The "European" procaine group showed more improvement than did the "American" procaine group. The differences in improvement scores were significant at the .007 level for psychiatric ratings. No significant differences were found for psychologic ratings or the nurses' ratings. Relatives' ratings showed a trend favoring the "European" group, which did not quite reach significance. Several statistical analyses were involved. An overall score was obtained from the ratings which demonstrated that 49.1 percent of the "European" group showed improvement in contrast to 19.4 percent of the "American" group. No statistical control for differences in initial states was attempted. Attrition was large; one-third of the group finally was selected for study. Psychologic tests could not be administered. The ratings were impressionistic and the variables rated were global, ambiguous, and somewhat redundant. Only the psychiatric ratings showed a significant effect of "European" procaine.

Gordon et al (36) collected a wide variety of physiologic measures obtained on the same group as the Abrams et al (82) sample. Measures included urinary 17-ketosteroids, 16-hydroxy steroids, uric acid, urea nitrogen, inorganic phosphate, pulmonary ventilatory functions, and motor-nerve conduction velocity. Only 17-ketosteroids and motor conduction differed. The "European" group showed a greater decrease of 17-ketosteroids; motor conduction was increased in both samples. "Results of the present investigation do not justify the use of either procaine preparation as eutrophic treatment of the aged," was the conclusion that these investigators drew from the study.

SUMMARY OF DATA ON PROCAINE IN SENILE DEMENTIA AND CEREBRAL ATHEROSCLEROSIS

The results for patients with organic brain syndromes, particularly those with cerebral arteriosclerosis or senile dementia, do not indicate that any procaine preparation is particularly or consistently effective for these disorders. Results of the more adequately controlled studies were generally negative for procaine; the findings of Abrams et al (82) and of Gordon et al (36) for "European" procaine were at best equivocal. The studies reporting clearly positive findings usually were either less well controlled or without controls.

PROCAINE IN CHRONIC DISEASE OF MIDDLE AND LATER LIFE

Much of the literature on the beneficial effects of procaine is concerned with such common chronic diseases as atherosclerosis, parkinsonism, chronic obstructive pulmonary disease, rheumatoid arthritis, osteoarthritis, high blood pressure and senile keratoses. Bodily changes common in aging (though probably not specific diseases) are also frequently addressed in the same literature. These include depigmentation and loss of hair, wrinkling and atrophy of the skin, reduction in sexual interest and function, and decline in strength and endurance.

There is little reason to doubt that thousands of elderly people who have been treated at the Geriatric Institute in Bucharest do indeed report that they feel better and do look better to physicians. The modes of treatment commonly employed at that institution include a good diet, vitamin and mineral supplements, application of the interest and care of well motivated persons in the health professions, the company of other old people, an atmosphere radiant with hope and empathy, and the administration of a drug for which patients and staff have the highest expectations. A central question about the efficacy of Gerovital may be phrased in this way: Do the pharmacologic effects of procaine contribute to the benefits of all other measures employed at the same time?

PROCAINE EFFECTS ON ARTHRITIS

In 1949, encouraged by the work of Parhon and Leriche, Aslan began to use intra-arterial injections of procaine in patients with arthritis and

arthrosis. The usual method of administration consisted of 0.10 gm of procaine in the form of a 1 percent solution injected directly into the artery supplying the joint. By 1956, 50 patients, not all elderly, had been treated by this method, with results that were described as excellent (83).

In 1951 Aslan began to use procaine intramuscularly for the severe degenerative diseases of old age, including arthritic disease, both degenerative and rheumatic. The usual dosage schedule consisted of 5 ml of a 2 percent solution three times weekly in a series of 12 injections with a ten-day interval in between. By 1960, several hundred arthritic patients had been treated. Restoration of joint mobility, reduction of pain, decrease of contractures, increase in muscle strength, and improvement in periarticular functions were reported (83–86).

In parallel with these clinical observations, an animal model of experimental arthritis was studied. Modifying the method of Selye, the investigators injected formalin into the joint space of the white rat and both therapeutic and prophylactic benefit was claimed (87) for procaine by Aslan and her colleagues.

Since 1951, procaine, usually by the intramuscular route, has been employed in a number of countries as a treatment for rheumatoid arthritis and osteoarthritis, rheumatoid spondylitis, psoriatic arthritis and other musculoskeletal disorders. The regimen has usually been that of Aslan, although in some cases the procaine employed had a higher pH than that preferred by Aslan. Scardigli and Guidi (69) reported a decrease in articular pain after procaine in 55 patients. Similar results were noted by Aslan when a 2 percent solution was infused into the arteries supplying diseased joints in 20 subjects. The Roumanian group seems to prefer the intra-arterial route when arthritic disease is the major problem, but the intramuscular route when multiple system disease is present.

Other authors have employed procaine according to Aslan's method and reported improvement in arthritic symptoms in nearly all cases. These include Destrem (88), Letourmey (66), Tchebotarev (89), Oury and Duche (90), and Kohler and Mampel (91). More recent contributions from Roumania, all of them enthusiastic about the benefits of procaine in joint disease, have appeared regularly over the years (83, 92–94).

Not all the reports are positive, however. Paule (62) found no x-ray changes in a patient with osteoarthritis of both hips but observed that the subject voluntarily took fewer drugs for pain. Kant and Sterne (74) noted no improvement in joint function in 20 elderly persons, and Fee and Clark (79) had no success treating 65 elderly persons. Luth (95) found no improvement of joint disease after procaine in 470 old people, and O'Connell and Offner (72) reported negative results in 10 patients. Gericke et al (71) treated 39 state hospital patients and observed not only no clinical improvement, but more abnormalities in x-ray films of the joints.

In one of the rare partly controlled studies with procaine, Smigel et al (51) found that procaine was beneficial. However, the protocol was changed in the middle of the trial, the coding of preparations was inadequate, and a flu epidemic struck the patients in the middle of the trial, so the results mean little or nothing.

In the past 15 years, a number of well designed and executed controlled clinical trials of drugs in arthritic diseases have been carried out. Essential to obtaining significant results are a number of elements in the trial. The criteria for disease must be rigidly defined, and the reliability and validity of the diagnosis determined. Rheumatoid arthritis, for example, has been defined in terms of morning stiffness, pain on motion or tenderness in at least one joint observed by a physician, swelling of joints, subcutaneous nodules, specific x-ray changes, positive results with agglutination tests, and characteristic changes in synovial membranes (96). Restriction categories such as the rash of disseminated lupus erythematosus, scleroderma, clubbing of the fingers, evidence of sarcoid or of infectious joint disease help to increase the precision of trials based on these criteria. The activity of the disease should be carefully determined before, and at intervals after treatment by such standard measures as questionnaires, grip strength testing, time required to walk a specific distance, degree of swelling, tenderness, and pain on passive movement of each afflicted joint, x-ray studies and erythrocyte sedimentation rate (97). There is agreement that trials must be double-blind, with a code that cannot easily be deciphered by those making judgments about improvement. Placebos and standard agents as controls are usually necessary. Methods of assessing joint status before and after treatment should be standard, participation rates should be high and dropouts low, both nonparticipation and dropout problems should be clearly described, and their potential effects on the trial should be carefully considered. The

method of analysis of results should follow logically from the protocol and rest on sound biometric and clinical principles (98–100).

There is not a single paper on the effect of procaine in an arthritic disease which contains even two of these requirements for an interpretable clinical trial. Aslan herself writes (83) that bone remineralization and increased joint spaces are important in evaluating procaine therapy. But most of her numerous reports contain no systematic descriptions of x-ray findings before or after procaine administration, or any other objective findings for that matter, except grip strength in some cases. Even when grip-strength measures were used, the reports indicate no concern about the reliability of the measure and no appreciation of the effect that motivation or fluctuations in hand pain can have on grip strength.

Procaine has been given for 26 years to thousands of arthritic patients, and the quality of the work is such that it is not possible to state whether the agent is beneficial or not. With few exceptions, the papers claiming that procaine is worthless as a treatment for arthritis are not substantially better than those claiming the drug is beneficial.

PROCAINE EFFECTS ON SKIN AND HAIR

Aslan (93) in 1951, while studying the effects of procaine on experimental arthritis in the rat, noted that the furry coats of the animals were improved. This led to her long-term observations on procaine in man and to a study of the effects of the drug on skin and hair as a major focus of those observations. There is some rationale for believing that procaine may have a beneficial effect on the skin. It dilates cutaneous vessels and raises skin temperature in acute experiments (1).

In a series of articles, the Roumanian group described their observations on procaine both in diseases of the skin and in the usual changes in the skin and hair with aging (64, 83, 84, 93, 94). They reported that skin turgor and color were improved and that hair regained pigment and sometimes regrew in previous areas of hair loss. A large number of skin diseases were also benefited from procaine. These included vitiligo, scleroderma, ichthyosis, psoriasis, and senile keratosis. In a few cases serial photographs illustrating the skin and hair changes were included in the publications. Aslan and colleagues reported that the skin and hair changes were among the most consistent and striking beneficial effects of procaine in their extensive experience.

Others agreed with the Roumanian investigators about the effects of procaine on the skin and hair changes of the usual aging process (49, 66, 71, 72, 101, 102) and in specific skin disorders (103). One critical observer, who doubted many of the alleged benefits of procaine, believed that skin appearance and muscle turgor were improved (104). However, as with all other effects of procaine in this literature, some authors believed that there were no beneficial effects on the skin (74, 78, 79). These negative trials were all double-blind and placebo-controlled, and in one of them repeated standard colored photographs showed no benefit from procaine (79).

One group of observers noted that skin turgor improved both in patients receiving procaine and in those receiving repeated injections of saline solution in another double-blind placebo-controlled study of 107 old women (50). The authors believed that repeated intramuscular injections alone over a long period of time may have had some beneficial effect on the skin. They offered no explanation of the mechanism.

If procaine has an antidepressant effect or if patients are hopeful about effects of treatment, this characteristic alone may explain some or all of the alleged beneficial effects on skin and hair. With improved appetite, both weight gain and increase in subcutaneous fat may make the skin look better. Combed hair, especially if water or hair-grooming preparations are used, looks darker than unkempt hair. People who are not depressed will wash and comb their hair, get haircuts, smile more, and have brighter eyes. Women free of depression are more likely to use cosmetics. All these factors can make the skin and hair look better. It is not necessary to postulate a trophic effect of procaine to explain them.

The spontaneous regression of skin lesions has not been studied thoroughly. Vitiligo is reversible in a small proportion of cases (perhaps 10 percent), and occasionally senile keratoses, actinic keratoses, or lentigo may also regress (105, 106). The extent to which such spontaneous regression may have influenced the results with procaine is conjectural.

PROCAINE EFFECTS ON HYPERTENSION

The known effects of procaine include both lowering and raising of the blood pressure. Procaine has a direct vasodilator action, best studied in skin and skeletal muscle (1). The effect is quite

transient. Procaine has sympatholytic properties (1) and diethylaminoethanol exhibits hypotensive effects of short duration. On the other hand, repeated intravenous injections of large doses of procaine in rabbits produces significant increases in hemoglobin levels and smaller increments in erythrocyte counts (107). Such effects may be expected to increase blood viscosity and therefore raise peripheral resistance and blood pressure. Furthermore, weight gain after procaine therapy in man is described as one of the more consistent effects (99–101, 108–112). This ought to raise blood pressure in some cases in view of the well known correlation between weight and blood pressure (113). Aslan and Vrabiescu (85, 114) noted opposing effects of procaine on blood pressure in the dog. Intra-arterial injections lowered pressures but intravenous injections increased sensitivity to adrenalin.

The reported effects of procaine on blood pressure in hypertensive patients likewise vary. Aslan, whose experience is most extensive of all, reported that a drop in blood pressure is common (108, 112). Oury and Duche (90) observed decreased pressure in 20 old people with hypertensive and cardiorespiratory disorders. Nebo also reported lowering of blood pressure in preliminary observations on 86 elderly patients (101) and in more numerous observations on 1985 patients seven years later (109). Bucci and Saunders (48) observed a drop in blood pressure in 5 of 6 hypertensive patients but in no normotensive patients after procaine treatment.

Negative reports on the effectiveness of procaine as an antihypertensive agent are almost as numerous as positive reports. For example, 86 old patients treated with procaine (Seurocaine) exhibited no change in blood pressure (115). Negative results were also described in a study of 34 patients (78) and in observations on 75 older persons treated with procaine (91).

The data on blood pressure in the articles on procaine are negligible. Usually there is simply a sentence or two indicating that the authors observed a fall or no change in blood pressure. No raw data or analyses of results are presented. The method of measuring pressure is not described and the time, frequency and circumstances of the measurements are not reported. Factors known to affect blood pressure acutely are fear, pain, a full urinary bladder, a heavy meal, body position, appearance and attitude of the examiner, hearing acuity of the observer, rate of fall of Hg in the manometer, digit preference and several others (116–119). There is no evidence that these factors were taken into account in the observations with procaine.

A controlled clinical trial of a potentially effective antihypertensive agent is one of the most difficult of all therapeutic studies to carry out. The recent Veterans Administration trials in the United States (118, 119) enumerate many of the relevant problems. The information on blood pressure changes in the reports on procaine in no way constitutes any kind of disciplined evaluation of antihypertensive effects. Procaine may or may not lower blood pressure. The truth of the matter is not in sight.

PROCAINE EFFECTS ON SEXUAL AND ENDOCRINOLOGIC FUNCTION

Procaine has been reported to be beneficial in the management of several kinds of sexual dysfunctions in men and women. Destrem (88) stated that 17 of 17 persons with depression, weakness and sexual problems were helped, and Portias (115) observed improvement in sexual interest and capacity in some of 86 persons treated with procaine. Aslan et al (120) reported a 9 percent increase in egg production in hens treated with 10 mg/kg of procaine daily as compared to a control group, but it is impossible to determine from the abstract if the difference in egg production was statistically significant.

Whereas some publications limit themselves to ascribing an estrogenic and androgenic effect to procaine (66, 112) or to procaine combined with multiple vitamins and magnesium pantothenate (121), some from the Bucharest Institute of Geriatrics are more explicit. Against the background of an extensive morbidity survey (122), Aslan reported some details of procaine effects on endocrine glands (83). She stated that vaginal smears have shown that small amounts of estrogen appear to be circulating in old women. Stimulation of pubic-hair growth with normal sex distribution and improved testicular function were also listed as effects of procaine. In some cases, Aslan noted that genital atrophy in elderly women was slowed and in others a return of normal appearance of the vulvovaginal mucosa and repigmentation of the labia minora occurred. Three cases of amenorrhea in women aged 35–40 were successfully treated by one or two series of intramuscular procaine injections, and several cases of failure to conceive were likewise successfully treated.

All the work performed with procaine in this field consists of preliminary observations which

did not reach the point of controlled clinical trials. The specific endocrine or sexual problems are not described in detail. Relevant histories on pregnancies, deliveries, frequency of sexual intercourse, and degree of sexual interest and function are not specified. Moreover, except for the paper on chickens (120), there are no attempts to follow an experimental protocol. It is appropriate again to state only that procaine may or may not have beneficial effects in endocrine and sexual function. The data are inadequate to support any conclusions.

PROCAINE EFFECTS ON ATHEROSCLEROTIC DISEASE

One of the most important issues about procaine is whether it prevents, delays, or reverses the atherosclerotic process. A closely allied and equally important question is the extent of its benefit on the clinical forms of atherosclerosis, myocardial infarction, angina pectoris, peripheral vascular disease, atherosclerosis of the head and neck, brain infarction, the lacunar state, and pseudobulbar palsy. The literature on procaine deals with both these issues.

Aslan and her colleagues attempted both laboratory and clinical research on the effects of procaine in atherosclerosis. They believed that Starling's concept of transcapillary permeability of proteins (123–128) needs modification. In studies on the effect of aging on capillary filtration of proteins, the differential filtration of serum proteins in atherosclerosis and the influence of prolonged procaine administration upon capillary filtration of proteins, they concluded that atherosclerosis was associated with reduced capillary permeability and that the process was reversed by procaine's permitting an extracellular fluid enriched with serum proteins to bathe tissues. A modified view of this hypothesis is presented elsewhere by Aslan (126). She also believed that the normal function of the vascular endothelium is lost in aging so that, in the elderly, larger molecules such as serum proteins are permitted to penetrate the vascular wall (127). She suggested that aged vascular endothelium permits both albumins and globulins to enter the vessel wall and that procaine selectively inhibits filtration of gamma globulin and enhances the filtration of albumins.

The Roumanian group induced atherosclerosis in rabbits by cholesterol feeding and studied the aorta and blood lipids in a control group and in a cholesterol-fed group, part of which was treated concomitantly with procaine intramuscularly (128). They reported that procaine inhibited aortic atherosclerosis after cholesterol feeding and had the effect of increasing alpha lipoproteins and decreasing beta lipoproteins when compared with the cholesterol-fed animals not treated with procaine. The data were not presented in sufficient detail to determine if the effects were significant. Similar results were reported by David (129).

The Roumanian group has maintained that procaine therapy in elderly men has been followed by an increase in the serum cholesterol level (64, 83, 104, 129). They attributed this to a mobilization of lipid from atherosclerotic plaques and fat depots. Other authors have reported no change or a decrease in serum cholesterol concentration after procaine treatment (51, 66, 71, 80, 115). In one study, the cholesterol level rose if it was low before treatment and fell if it was high (130). In living man, it is impossible to tell what happens to atherosclerotic plaques except by such procedures as serial coronary angiography — procedures which are unjustified in such a situation. In a series of papers reporting increasing numbers of observations over longer periods of time, the Roumanian group described improvement in the atherosclerotic diseases (83, 86, 94, 126, 131). In these accounts, peripheral arterial circulation was improved and intermittent claudication reduced. Anginal attacks were reduced in frequency, myocardial infarction was improved, and digitalis requirements in patients with congestive heart failure were reduced. They also cited unexpected return of muscular strength and dexterity after stroke, diminution of the symptoms of the lacunar state and pseudobulbar palsy, and beneficial effects on disorders more difficult to define (e.g., cerebral atherosclerosis and cerebral angiospasm). This experience now extends to many thousands of patients treated for as long as 24 years.

Other authors have reported favorable results in diseases related to atherosclerosis. Nadel (132) observed improvement in peripheral circulation, generalized atherosclerosis, pseudobulbar palsy and the shoulder-hand syndrome after percutaneous procaine blockade. Vascan et al (133) noted beneficial effects in 127 elderly patients with similar disorders and with cerebral hemorrhage as well. Portias (115) observed moderate improvements in generalized atherosclerosis after procaine, and Letourmy (66) following Aslan's method found lessened angina, reduced intermittent claudication and regression of hemiplegia

and spastic states during procaine therapy. A similar favorable effect was observed on angina and intermittent claudication in 86 middle-aged and old persons after procaine by Nebo (109). Lassman and Plenck (134) were impressed with the beneficial effects of procaine given orally in cerebral atherosclerosis. Tsoukas and Papantoniou (135) believed that procaine helped recovery from cerebrovascular attacks, and advocated its use. Hartin (136) reported that 80 percent of 243 middle-aged and elderly persons were improved or exhibited stabilization of their disease when procaine was employed to treat various cardiovascular disorders. Paule (62) noted improvement after procaine in 6 elderly patients with heart failure. Dryagin (137) noted beneficial effects of procaine in 200 patients with cerebral atherosclerosis.

There are also many studies in which no improvement in atherosclerotic diseases occurred after procaine. Tchebotarev (89) warned that patients felt better and were more active after procaine treatment but their electrocardiograms (ECGs) became worse. Scardigli and Guidi (69) could not confirm beneficial effects of procaine in 76 elderly patients treated 12 to 15 months for cerebral atherosclerosis. O'Connell and Offner (72) reported improved mood but unchanging atherosclerotic disease in 30 elderly persons. In two well controlled clinical trials, Hirsch (78) and Kant and Sterne (74) observed no change in the manifestations of cerebral atherosclerosis or in the ECG. Siggelkow (138) observed that symptoms attributable to cerebral ischemia improved only temporarily.

With a few exceptions, all the reports on the effect of procaine on the atherosclerotic process and on the clinical manifestations of atherosclerosis can only be described as preliminary, sketchy, unstructured, and almost completely uninterpretable. Generalized atherosclerosis and cerebral atherosclerosis, two conditions reported improved by procaine, are diagnostic wastebaskets; the criteria and manifestations vary widely from physician to physician. In any definitive study, angina pectoris, intermittent claudication, cerebral infarction, congestive heart failure, myocardial infarction and related terms require precise definitions of known reliability applied in a standard manner (139). Because angina pectoris and intermittent claudication are usually diagnosed from the medical history alone and can be improved by placebos, controlled clinical trials with double-blind placebo-controlled methodology are essential. Return of the function of muscle groups after stroke depends in part on the patient's morale and sustained effort and can be influenced by such nonspecific beneficial factors as: attention from a variety of persons in the health professions; emotional support from the family, friends and other patients; and an optimistic attitude. Without disciplined clinical trials, it is impossible to separate these effects from those of procaine.

In the early stages of the work with procaine, lipid transport and the atherosclerotic process were poorly understood. Recent improvements in technology (including paper electrophoresis, the preparatory ultracentrifuge, and the autoanalyzer) and the increase in our knowledge of lipid transport disorders and the atherosclerotic processes have been substantial (140-142). The limitations and inaccuracies in some of the usual laboratory methods of measuring cholesterol have become apparent. We have learned that blood lipid concentrations may vary with diet, alcohol intake, and psychosocial stress (143) and that only carefully controlled clinical trials can indicate benefit to the atherosclerotic process (144). None of these advances in methodology, with the partial exception of paper electrophoresis, has been employed in the studies of procaine and atherosclerosis. We must conclude that the work performed so far does not permit any decision as to whether or not procaine is beneficial in atherosclerotic disease.

PROCAINE EFFECTS ON OTHER DISORDERS

A relatively small number of reports deal with the beneficial effects on peptic ulcer, chronic pulmonary disease, parkinsonism, ulcerative colitis, asthma, and longevity (64, 83, 145, 146). Because of the paucity of data, no survey of the effects of procaine in these disorders is attempted, although the atropine-like effects of procaine provide a rationale for its benefit in these disorders.

There has also been relatively little published about the effects of procaine on the lifespan. In two reports (145, 147), Aslan and David claimed that procaine lengthened the life of the rat. In a controlled trial of the effects of procaine, PABA and DEAE on the rodent lifespan, Verzar (47) observed no beneficial effects on survival, body weight at death, or on thermic contraction of tendons. Another aspect of Verzar's work is worth citing. Among the control rats for the procaine group, 50 percent survived 708 days and 20 percent survived 900 days. Among the control

rats for the PABA group, 50 percent survived 866 days and nearly half lived 900 days or longer. With this kind of variation in lifespan between two groups of control rats, the need for precise design and careful analysis of such experiments is demonstrated.

A study of the effects of procaine on human longevity is a complex issue. It involves sensitive, precise and long-term follow-up of such a large number of subjects, and the published data are so meager, that no discussion is warranted here.

Over the past three decades, the methods of controlled clinical trials have evolved to the point of becoming standard (148). First the disease to be treated must be given an explicit definition, and it must be demonstrated that several observers agree on independently-made diagnoses in a number of patients. Then the characteristics of patients recruited for the trial must be determined. Such characteristics include age range, sex, socio-economic status, severity of disease and method of recruitment. The patients, after giving informed consent, are categorized by severity of disease — and possibly other characteristics — and members of each category are randomly assigned to receive a drug believed to be active, or an inert preparation. It may be desirable to administer both preparations, drug and placebo, to all participants in random order. Neither the patient nor the experimenter should know what any participant is receiving. The double-blind methodology requires that drugs be coded by an identifying system that can be consulted only in cases of suspected drug toxicity. Care must be taken to ensure that participants are taking their medicines, and the dropout rate must be minimized. Those who collect the data on which a judgment of effectiveness is to be made must also be unaware of what any subject is receiving. Finally, the results must be subject to disciplined statistical analysis of a type determined before the beginning of the trial. All aspects of the clinical trial should be explicit so that the work may be repeated exactly.

SUMMARY OF PROCAINE EFFECTS ON CHRONIC DISEASES

There is little reason to doubt that many patients have been treated at the Geriatric Institute in Bucharest and have felt and looked better. However, there is no compelling reason to believe that procaine, aside from a possible antidepressant effect, contributed to this improvement. The evidence that procaine has a prophylactic or therapeutic effect in aging or the diseases of later life is unconvincing. The drug has been used for these purposes for 24 years in over 100,000 patients, and there is still no sound evidence upon which to conclude that it has value.

CONCLUSIONS

This review of the literature yields no convincing evidence that, except for a possible antidepressant effect, the systemic use of procaine (or Gerovital, of which the major component is procaine) is of value in the treatment of diseases in older patients.

The literature on procaine reveals that the quality of clinical trials of new agents in the treatment of the elderly may be very poor. There is need for conferences and symposia to discuss the current status of evaluating new drugs in the elderly and the special problems of clinical trials in the aged.

If procaine has an antidepressant effect, there is some likelihood that this may account for the impression among some observers that in procaine-treated patients there is a decrease of complaints attributable to the musculoskeletal, cardiovascular, endocrine, sexual, gastrointestinal and respiratory systems. Depression may play a greater role than previously suspected in these multiple discomforts of the elderly. Controlled clinical trials of standard antidepressant drugs among aged persons deserve careful consideration.

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BRIEF COMMUNICATION

DREAM RECALL AND THE CONTRACEPTIVE PILL

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Data collected on women students at Edinburgh University allowed a comparison to be made between those who were taking a contraceptive pill and those who were not. The evidence suggests that women taking a contraceptive pill are more likely to recall dreaming, and that it is the progestagenic component that is the more active one. However, the data collected do not exclude the possibility that the differences observed are the consequence of other psychosocial variables; further research is recommended.

In a recent survey of students registered for study at Edinburgh University for the 1974 to 1975 session, data were collected on reported rates of dream recall. For the women in the population, information was also sought on their menstrual cycle characteristics, and, for those taking a contraceptive pill, the brand name of the pill and the length of time it had been taken.

Altogether, the women listed over 30 different varieties of contraceptive pill that were being taken, but, of these, only eight were in common use. On the basis of their active chemical constitutents, these fall into four groups,

Group	*Estrogenic Component*	*Progestagenic Component*
I (Ortho-Novum 1/50, Norinyl)	Mestranol	Norethindrone
II (Minovlar, Gynovlar 21)	Ethinyl estradiol	Norethindrone
III (Ovran, Eugynon 30, Microgynon)	Ethinyl estradiol	D-Norgesterel
IV (Minilyn)	Ethinyl estradiol	Lynestrenol

When the data were examined for effects of the contraceptive pill on dream recall, we found a number of differences, which are summarized in Table 1.

As the table shows, women taking a contraceptive pill are more likely to report frequent recall of dreaming. Moreover, comparison between the various pill groups allows us to examine possible effects of the various active components. If we compare responses for women taking a pill from groups I and II, we can examine the effect of the two different estrogens (since both have the same progestagen). The actual frequencies for "frequent" and "infrequent" recall of dreams are given in Table 2. As the figures suggest, there is no discernible difference in the reported frequencies of dream recall for women taking a contraceptive pill from either of these groups. However, if we compare women taking contraceptive pills from groups II and IV, or II and III, we can compare the effects of the different progestagens (since they all contain the same estrogenic component). As the frequency distribution in Table 3, comparing groups II and IV, shows, although not statistically significant at the 5 per cent level, there is a difference between the two groups (and this is also true for the group II and group III comparison).

Taken together, these findings cast further light on the possible role of hormones in affecting dream recall. An earlier study by the authors showed that despite other variations in recall through the menstrual

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TABLE 1
Dream Recall Frequency in Relation to the Contraceptive Pill

Contraceptive Pill	Dream Recall (%)			Ratio Frequent/ Infrequent	N
	Frequent	Intermediate	Infrequent		
Group I	44.3	33.3	22.4	1.98/1	183
Group II	45.1	30.4	24.5	1.84/1	184
Group III	37.2	34.6	28.2	1.32/1	78
Group IV	34.8	37.6	27.7	1.26/1	141
Respondents not taking contraceptive pill	28.1	34.1	37.9	.74/1	2316

TABLE 2
Dream Recall and Pill Groups: Comparing Different Estrogens

Women Taking Pill from:	Dream Recall		Components
	Frequent	Infrequent	
Group I	81	41	(Mestranol + norethindrone)
Group II	83	45	(Ethinyl estradiol + norethindrone)

TABLE 3
Dream Recall and Pill Groups: Comparing Different Progestagens

Women Taking Pill from:	Dream Recall		Components
	Frequent	Infrequent	
Group II	83	45	(Ethinyl estradiol + norethindrone)
Group IV	49	39	(Ethinyl estradiol + lynestrenol)

cycle, women recall more dreams in the few days preceding menstruation (2), an observation supported by other studies (1, 3). Such a change in recall might seem to indicate the importance of progesterone in increasing recall, as this peaks at this time. In the case of women taking a contraceptive pill, we have a control on hormone levels; our findings suggest that it is the progestagenic component that has the more marked effect, which, in turn, would also explain the higher overall recall reported by women taking a contraceptive pill; as they have an appreciable amount of progestagen on all of the days that they are actually taking the pill. In other words, the data indicate that progesterone, and the related progestagens, improve dream recall. One corollary of this should be increased recall for women during pregnancy, and we hope to examine this in future research.

Some caution must be advised in advancing a wholly physiological explanation of the differences observed in the data, however. Takers and nontakers of the pill may differ in significant respects which could also affect dream recall and for which data are not available, including such psychosocial factors as religious affiliation, nature and degree of socialization, intellectual bias, or marital status. Equally, differences between pill types may be a consequence of differences between those willing to use new varieties of contraceptive pill, and those who continue to use the same variety. In relation to this, no effects were found stemming from the length of time that the pill had been taken. Nonetheless, the data do suggest the value of further research on the effects of the contraceptive pill, and progestagens in particular, on dream recall.

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Reversal of Central Anticholinergic Syndrome by Galanthamine

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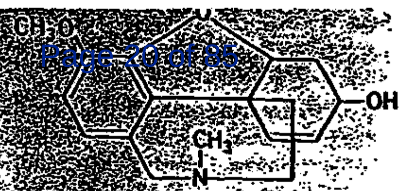

Fig 1.—Structural formula of galanthamine hydrobromide, a tertiary amine derivative of phenantridine.

• Ten volunteers were given 2 mg scopolamine intravenously (IV) to produce substantial drowsiness and sleepiness. Galanthamine, 0.5 mg/kg IV, effectively reversed the central anticholinergic syndrome produced by scopolamine. Electroencephalographic monitoring of two subjects matched the observed changes of consciousness: scopolamine replaced the dominant awake alpha rhythm with a disorganized, slow, 4- to 6-Hz activity. Galanthamine promptly returned the EEG pattern to the control, awake state.

Galanthamine produces effective, safe, and long-lasting reversal of the central anticholinergic syndrome in man.

(*JAMA* 238:2293-2294, 1977)

GALANTHAMINE is a naturally occurring anticholinesterase extracted from the snowdrop flower (*Galanthus nivalis*), which grows wild in Bulgaria.[1] The phenantridine derivative (Fig 1) has been used clinically to reverse nondepolarizing neuromuscular blockade.[1]

Experimentally, galanthamine inhibits not only muscle, but also brain cholinesterases.[2] The drug is a tertiary amine that crosses the blood-brain barrier; thus, like physostigmine, it might reverse the central anticholinergic syndrome produced by scopolamine and related anticholinergic compounds.[3]

Methods

Ten healthy male medical students volunteered to undergo the study. Informed consent was obtained from each after the nature of the procedure had been fully explained. The investigation was carried out in a quiet, semidarkened room, with the volunteer resting comfortably in the supine position. Lactated Ringer's solution was infused intravenously (IV), with drugs injected via the running infusion.

All ten volunteers received 2 mg of scopolamine hydrobromide IV; central effects such as drowsiness, disorientation, and hallucination were observed at regular intervals. After 40 minutes, 0.5 mg/kg galanthamine hydrobromide was given IV to reverse the central effects of scopolamine.

A standard EEG was recorded intermittently in two of the volunteers.

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Results

In all volunteers, the intravenous injection of scopolamine (2 mg) resulted in drowsiness within ten minutes, reaching peak effect after 30 to 40 minutes (Fig 2). Drowsiness was sometimes associated with disorientation, visual hallucinations, and delirium.

Injection of galanthamine hydrobromide, 0.5 mg/kg IV, rapidly reversed the central effects of scopolamine. Subjects became alert within five to ten minutes, and were completely awake after 30 minutes (Fig 3).

The pulse rate increased following scopolamine administration, from a control of 60 to 80 beats per minute to 110 to 130 beats per minute. After galanthamine was given, the heart rate returned to 60 to 70 beats per minute.

Two hours later, the volunteers were invited to review their experience. They were completely oriented and suffered no relapse of drowsiness. In fact, they felt more alert than usual, and did not feel at all sleepy the night of the experiment.

The EEGs in two awake volunteers showed normal background 9- to 11-Hz alpha rhythm in the posterior leads. Within ten minutes following scopolamine injection, definite EEG changes associated with drowsiness became evident, reaching their maximum effect after approximately 30 minutes. Changes comprised replacement of the dominant alpha rhythm by disorganized, slow 4- to 6-Hz activity of moderate to low amplitude. Intravenous galanthamine promptly and permanently reversed the EEG pattern to the control.

Fig 2.—Sleeping volunteer 30 minutes after intravenous injection of scopolamine hydrobromide, 2 mg.

Fig 3.—Complete awakening ten minutes after injection of galanthamine hydrobromide, 0.5 mg/kg.

Comment

Many data support the hypothesis that cholinergic mechanisms are involved in states of wakefulness and sleep. Cholino-reactive structures are widely distributed throughout the ponto-mesencephalic reticular formation. Scopolamine and related anticholinergic compounds that cross the blood-brain barrier can result in the central anticholinergic syndrome characterized by drowsiness, disorientation, delu-

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sions, and hallucinations. The mechanism by which anticholinergics produce central depressant and behavioral effects probably is the inhibition of cholinergic systems, resulting in a functional imbalance.

Physostigmine, a tertiary amine acetylcholinesterase inhibitor, can cross the blood-brain barrier and thereby reverse the central depression caused by overdoses of anticholinergic drugs,[4] phenothiazines,[5] tricyclic antidepressants,[6] and buterophenone derivatives.[7] The present report shows that galanthamine, another tertiary amine anticholinesterase, also can rapidly cross the blood-brain barrier and effectively reverse the central anticholinergic syndrome caused by scopolamine overdosage.

The site of action of cholinergic agonists (anticholinesterases) and anticholinergic agonists (anticholinergics) is probably the midbrain reticulum. Evidently, galanthamine as well as physostigmine can inhibit brain acetylcholinesterase activity and produce marked EEG activation. The EEG activation is dependent on the degree of acetylcholinesterase inhibition in the pontomesencephalic region of the brain.[8]

Physostigmine has been used clinically to reverse the central anticholinergic syndrome. However, its relatively short duration of action has resulted in relapse of drowsiness after the initial arousal.[3] The alkaloid is rapidly destroyed in the body by hydrolytic cleavage at the ester linkage by plasma cholinesterases. Galanthamine, on the other hand, is a hydrolysis-resistant phenantridine derivative that can be used clinically to produce an effective and long-lasting reversal.

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Familial Lupus Erythematosus

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The child of a woman with discoid lupus erythematosus (DLE) had lesions of DLE develop at the age of 2 months. The original lesions persisted and new lesions continued to develop to date; the child is now 28 months old. In a second child, now 11 months old, a probable lupus erythematosus rash developed at 1 week of age.

(*JAMA* 238:2294-2296, 1977)

LUPUS erythematosus (LE) presenting within the first year of life is relatively uncommon.[1-12] All of the cases reported, except that of Grossman et al,[1] showed signs of lupus at birth or shortly thereafter.

We have had the opportunity to follow the course of a family in which three members have lupus erythematosus. The proband, a 28-month-old boy, had discoid-type lesions since 2 months of age (Fig 1-3). This is the earliest reported case of a child with persistent skin manifestations of lupus erythematosus. The proband's 24-year-old mother has an 11-year history of discoid lupus erythematosus. The second child is an 11-month-old girl who has an eruption on her face (since 1 week of age) that is clinically similar to that of her brother.

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Report of Cases

CASE 1.—A 3-month-old boy was first seen at the Skin and Cancer Unit on Dec 5, 1974. At the age of 2 months, he had an eruption that started on the cheeks and then appeared on the arms. The lesions began as red papules; some subsequently became crusted.

On physical examination, he was found to have erythematous, scaly, and crusted macules, and papules on the face and arms. He was thought to have impetigo and was treated with erythromycin for two weeks. When reexamined, no change in the skin lesions was found.

A biopsy specimen from the right forearm showed a moderately superficial and deep perivascular and periadnexal lymphohistiocytic infiltrate, with focal interface involvement by lymphocytes and histiocytes and some vacuolar alteration in the epidermis. These changes were interpreted to be compatible with those of lupus erythematosus, but not unequivocally diagnostic (Fig 4 and 5). Direct immunofluorescence tests on a skin section showed complement but no IgG at the dermoepidermal junction. A test for serum antinuclear antibody was negative. Other tests performed at this time (eg, complete blood cell count [CBC], hematocrit, platelets, urinalysis, ESR, two lupus erythematosus [LE] tests, and serum C3 and C4) showed results within normal limits.

On May 5, 1975, another skin biopsy specimen was taken. It showed a superficial and deep perivascular lymphohistiocytic infiltrate that obscured the dermoepidermal interface where there were numerous individually necrotic keratinocytes. The blood vessels of the superficial plexus were widely dilated and were surrounded by a few extravasated erythrocytes. The biopsy specimen was interpreted as showing probable discoid LE. Mucha-Habermann's disease was considered in a differential diagnosis.

Other tests with results within normal limits were light-testing for minimal erythema dose; antibodies to extractable nuclear antigen, single- and double-stranded DNA, and double-stranded RNA; and complete tests for complement. Six months later, the test for antinuclear antibody was repeated, with negative results.

At 28 months of age, new lesions are still developing on the arms and face. The lesions resolve with hyperpigmentation but leave no visible atrophy. Sunlight has caused exacerbations on several occasions. He has shown a variable response to topically applied corticosteroids and a good response to intralesional triamcinolone acetonide, 3 mg/cc.

CASE 2.—The mother, when first seen at

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Serial No.: 819,141 Group No.: 125

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JOHN RICHARDS

(Type or print name of person mailing paper)

(Signature of person mailing paper)

280.00-242—1

PTOL-85b (Rev. 5-85)

U.S. Department of Commerce
Patent and Trademark Office

ISSUE FEE TRANSMITTAL

This form is provided in lieu of a formal transmittal and should be used for transmitting the Issue Fee. Sections 1A through 4 must be completed as appr

INVENTOR'S ADDRESS CHANGE | SC/SERIAL NO.

INVENTOR'S NAME

Street Address

City, State and Zip Code

CO-INVENTOR'S NAME

Street Address

City, State and Zip Code

☐ Check if additional changes are on reverse side.

MAILING INSTRUCTIONS

All further correspondence including the Issue Fee Receipt the Patent, and advanced orders will be mailed to the address entered in section 1 on PTOL-85c, unless you direct otherwis by specifying the appropriate name and address in 1A below. (Note: See box 5 below for correspondence concerning maint nance fee payments.)

2A. The COMMISSIONER OF PATENTS AND TRADEMARKS is requested to apply the Issue Fee to the application identified below.

(Signature of party in interest of record) (Date)

Jan 15

Note: The Issue Fee will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the Patent and Trademark Office.

SC/SERIAL NO.	FILING DATE	TOTAL CLAIMS	EXAMINER AND GROUP ART UNIT	DATE MAILED
08/819,141	01/15/86	007	FRIEDMAN, S 125	10/20/86

First Named Applicant DAVIS, BONNIE

TITLE OF INVENTION METHOD OF TREATING ALZHEIMER'S DISEASE

ATTY'S DOCKET NO.	CLASS-SUBCLASS	BATCH NO.	APPLN. TYPE	SMALL ENTITY	FEE DUE	DATE DUE
U 5631	514-215.000	727	UTILITY	YES	1280.00	01/20/87

A. Further correspondence to be mailed to the following:

JOHN RICHARDS
c/o LADAS & PARRY
26 WEST 61st STREET
NEW YORK, N.Y. 10023
Reg. No. 31053 (212) 708-1915

2B. For printing on the patent front page, list the names of not more than 3 registered patent attorneys or agents OR, alternatively, the name of a firm having as a member a registered attorney or agent. If no name is listed, no name will be printed.

1 LADAS & PARRY
26 West 61 Street
2 New York, N.Y. 10023
3 (212) 708-1800

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ASSIGNMENT DATA (print or type) ATTENTION IS DIRECTED TO 37 C.F.R. 1.334

(1) ☒ This application is NOT assigned.
(2) ☐ Assignment previously submitted to the Patent and Trademark Office.
(3) ☐ Assignment submitted herewith.

For Printing On The Patent: (Unless an assignee is identified below, no assignee data will appear on the patent. Inclusion of assignee data below is only appropriate when an assignment has been previously submitted to the PTO or is submitted herewith. Completion of this form is NOT a substitute for filing of an assignment as required by 37 C.F.R. 1.334).

(1) NAME OF ASSIGNEE:

(2) ADDRESS: (City & State or Country)

(3) STATE OF INCORPORATION, IF ASSIGNEE IS A CORPORATION:

4. The following fees are enclosed: (x) Issue Fee [ ] Advanced order [ ] Assignment recording

Any additional

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5. All correspondence relating to maintenance fees will be addressed to the correspondence address unless a separate "Fee Address" is provided to the Patent and Trademark Office (37 CFR 1.363). A "Fee Address" may be submitted by the owner of record with the payment of the issue fee or thereafter by using form PTO-1537.

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PTOL-85c (Rev. 5-85)

ISSUE FEE TRANSMITTAL

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LESTER HORWITZ
C/O LADAS & PARRY
26 WEST 61ST STREET
NEW YORK NY 10023

2A. The COMMISSIONER OF PATENTS AND TRADEMARKS is requested to apply the Issue Fee to the application identified below.

(Signature of party in interest of record) — (Date) Jan 15 87

Note: The Issue Fee will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the Patent and Trademark Office.

	SC/SERIAL NO.	FILING DATE	TOTAL CLAIMS	EXAMINER AND GROUP ART UNIT	DATE MAILED
	06/[illegible]	01/15/86	[illegible]	[illegible] 125	10/[illegible]/86

First named applicant: [illegible] HORWITZ

TITLE OF INVENTION: METHOD OF TREATING ALZHEIMER'S DISEASE

	ATTY'S DOCKET NO.	CLASS-SUBCLASS	BATCH NO.	APPLN. TYPE	SMALL ENTITY	FEE DUE	DATE DUE
	U [illegible]21	514-210.000	12	UTILITY	[illegible]	$[illegible].00	01/20/87

Further correspondence to be mailed to the following:
JOHN RICHARDS
c/o LADAS & PARRY
26 WEST 61st STREET
NEW YORK, N.Y. 10023
Reg. No. 31053 (212) 708-1915

28. For printing on the patent front page, list the names of not more than 3 registered patent attorneys or agents OR, alternatively, the name of a firm having as a member a registered attorney or agent. If no name is listed, no name will be printed.

1 LADAS & PARRY
2 26 West 61 Street
~~New York, N.Y. 10023~~
3 (212) 708-1200

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ASSIGNMENT DATA (print or type)

(1) [X] This application is NOT assigned.
(2) [ ] Assignment previously submitted to the Patent and Trademark Office.
(3) [ ] Assignment submitted herewith.

For Printing On The Patent: (Unless an assignee is identified below, no assignee data will appear on the patent. Inclusion of assignee data below is only appropriate when an assignment has been previously submitted to the PTO or is submitted herewith. Completion of this form is NOT a substitute for filing of an assignment as required by 37 C.F.R. 1.334).

(1) NAME OF ASSIGNEE:

(2) ADDRESS: (City & State or Country)

(3) STATE OF INCORPORATION, IF ASSIGNEE IS A CORPORATION:

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Director for Patents
Washington, D.C. 20231

BOX PATENT EXTN

EXPRESS MAIL CERTIFICATE

"Express Mail" label number EL 728212517 US
Date of Deposit April 24, 2001

I hereby certify that the following attached paper or fee

Letter dated April 24, 2001, Check for $1,120.00, Power, 37 CFR 3.73(b) Certificate, Letter to Dr. Bonnie Davis, copy Merck Index, Copy '318 patent, copy (3) Maintenance Statements; Three copies of the above, Postcard

is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Director for Patents, Washington, D.C. 20231.

HUGH R WOTHERSPOON
Type or print name of person mailing paper)

(Signature of person mailing paper or fee)

Each paper, letter or communication relating to an international application during the international stage for which a date of filing is to be obtained as of the date of mailing must have its own certificate and the "Express Mail" label number as a part thereof or attached thereto. When, as here, the certification is presented on a separate sheet, that sheet must(1) be signed and (2) fully identify and be securely attached to the paper or fee it accompanies. Identification should include the serial number and filing date of the application as well as the type of paper being filed, e.g. complete application, specification and drawings, responses to rejection or refusal, notice of appeal, etc. If the serial number of the application not known, the identification should include at least the name of the inventor(s) and the title of the invention.

The label number need not be placed on each page. It should, however, be placed on the first page of each separate document, such as, a new application, amendment, assignment, and transmittal letter of a fee, along with the certificate of mailing by "Express Mail". Although the label number may be on checks, such a practice is not required. In order not to deface formal drawings it is suggested that the label number be placed on the back of each formal drawing or the drawings be accompanied by a set of informal drawings on which the label number is placed.

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April 24, 2001

Director of United States Patent and Trademark Office
Box **Patent Extension.**
Washington, D.C. 20231

Dear Sir:

Application for Extension of Patent Term of U.S. Patent 4,663,318 Pursuant to 35 U.S.C. Section 156 Extension of the Term of U.S. Patent 4,663,318 for a Term Expiring on December 12, 2008 is hereby requested for the reasons set out below:

Requirements Pursuant to 37 CFR 1.710

37 CFR 1.710(a) A patent is eligible for extension of the patent term if the patent claims a product as defined in paragraph (b) of this section, either alone or in combination with other ingredients that read on a composition that received permission for commercial marketing or use, or a method of using such a product ....

b) The term "A product referred to in paragraph (a) of this section means

1) The active ingredient of a new human drug, antibiotic drug ... (as those terms are used in the Federal Food, Drug and Cosmetic Act ....) including any salt or ester of the active ingredient, as a single entity or in combination with another active ingredient ...

U.S. Patent 4,663,318 in claim 1 thereof recites:

"1. A method of treating Alzheimer's disease ... which comprises administering ... galanthamine or a pharmaceutically acceptable acid addition salt thereof".

Galantamine hydrobromide has received permission for commercial use under application number NDA 21-169 for the treatment of mild to moderate dementia of the Alzheimer's type. Therefore, U.S. Patent 4,663,318 is subject to extension of the patent term.

Requirements Pursuant to 37 CFR 1.720

37 CFR 1.720(a) The term of a patent may be extended if the patent claims a product or a method of using a product as defined in 37 CFR 1.710.

U.S. Patent 4,663,318 in claim 1 thereof recites:

"A method of treating Alzheimer's disease ... which comprises administering ... galanthamine or a pharmaceutically acceptable acid addition salt thereof".

37 CFR 1.710 defines "a product" as "The active ingredient of a new human drug ... (as those terms are used in the Federal Food, Drug and Cosmetic Act ....") including any salt or ester of the active ingredient as a single entity or in combination with another active ingredient ..." Galantamine hydrobromide is the active ingredient which is found in the final dosage form prior to admininistration of the product to the patient for the drug "Reminyl®" which has received approval under application number

NDA 21-169. Thus, the U.S. '318 patent claims a method of using a product as defined in 37 CFR 1.710.

> ***37 CFR 1.720(b) The term of a patent may be extended if the term of the patent has never been previously extended except for extensions issued pursuant to sections 1.701, 1.760 and 1.790.***

U.S. Patent 4,663,318 has never been previously extended.

> ***37 CFR 1.720(c) The term of a patent may be extended if an application for extension is submitted in compliance with 37 CFR 1.740.***

We set out an explanation of how this application complies with 37 CFR 1.740 below.

> ***37 CFR 1.720(d) The term of a patent may be extended if the product has been subject to a regulatory view period as defined in 35 USC 156(g) before its commercial marketing or use.***

Galantamine hydrobromide (as "Reminyl®") has been subject to regulatory review under application number NDA 21-169. We set out below how the regulatory review period as defined in 35 USC 156(g) is calculated.

> ***37 CFR 1.720(e) The term of a patent may be extended if the product has received permission for commercial marketing or use and ... the permission for the commercial marketing or use of the product is the first received permission for commercial marketing or use under the provisions of***

law under which the applicable regulatory review occurred.

Galantamine hydrobromide has received permission for commercial use under application number NDA 21-169 for the treatment of mild to moderate dementia of the Alzheimer's type. This permission is the first received permission for galantamine hydrobromide for any use under the provisions of law under which the regulatory review occurred.

37 CFR 1.720(f) The term for patent may be extended if the application is submitted within the 60 day period beginning on the date the product first received permission for commercial marketing or use under the provisions of law under which the applicable regulatory review period occurred.

We make this showing under 37 CFR 1.740(a)(5) below.

37 CFR 1.720(g) The term for patent may be extended if the term of the patent including any interim extension issued pursuant to section 1.790 has not expired before the submission of an application in compliance with 37 CFR 1.741.

U.S. Patent 4,663,318 issued on May 5, 1987. Pursuant to 35 USC 154(c)(1) ' The term of a patent that is in force on.....the date that is 6 months after the date of the enactment of the Uruguay Round Agreements shall be the greater of the 20 year term as provided in subsection (a), or 17 years from grant subject to any terminal disclaimers'. The

relevant 'Uruguay' date is June 8, 1995. The US '318 Patent was in force on June 8, 1995. The term of 17 years from May 5, 1987 is May 5, 2004. The date of expiration pursuant to 35 USC Section 154(a)(2) is 20 years from the U.S. filing date of January 15, 1986 **i.e. January 15, 2006**. The greater term is the term which expires on January 15 ,2006. Therefore, the term of the patent has not expired before the date hereof.

> ***37 CFR 1.720(h) The term of a patent may be extended if no other patent term has been extended for the same regulatory review period for the products.***

No other application apart from this application for patent term extension has been filed based on the regulatory review period referred to herein.

Requirements Pursuant to 37 CFR 1.730

Application is submitted in respect of U.S. Patent 4,663,318. The owner of record of the U.S. '318 patent is Synaptech Inc.(hereinafter referred to as 'Extension Applicant') of c/o Schwartz and Salomon, 42nd Floor, 225 Broadway, New York, NY 10007-3001. Extension Applicant is owner of record by virtue of an Assignment made between Intelligen Corporation of P.O. BOX 157, Cold Spring Harbor, N.Y. 11724, USA (hereinafter referred to as 'Intelligen') and Extension Applicant dated the 30th day of November 1995 of record at Reel 8376 Frames 0935-0943. Intelligen is the assignee of Bonnie Davis of 17 Seacrest Drive, Huntington, New York, 11743,USA(hereinafter referred to as 'Inventor') by

virtue of an assignment made between Inventor and Intelligen and dated July 26, 1990 of record at Reel 5392 Frames 428-430.

The marketing applicant pursuant to Section 505 of the Federal Food, Drug and Cosmetic Act is Janssen Research Foundation (hereinafter referred to as "Marketing Applicant"). Marketing Applicant is a division of Janssen Pharmaceutica Inc., a Pennsylvania Corporation, which is a wholly owned subsidiary of Johnson and Johnson. Janssen Pharmaceutica NV a Belgian business corporation organized and existing under the laws of Belgium with its registered office at Turnhoutseweg 30,B-2340, Beerse, Belgium (hereinafter referred to as "Pharmaceutica") is Licensee of the patent pursuant to a License dated the 30th day of November, 1995 and made between Extension Applicant and Pharmaceutica. Pharmaceutica is also a wholly owned subsidiary of Johnson and Johnson. Thus, Marketing Applicant is related to Pharmaceutica (the Licensee of Extension Applicant) because each is a wholly owned subsidiary of Johnson and Johnson. Pharmaceutica is related to Extension Applicant through the License. The regulatory review period (the effective date of the IND permission) commenced on the 4th day of October, 1996 which is after the date of the License (November 30, 1995 (see above)). It can be seen that at all times during the regulatory review period there existed an agency relationship between Extension Applicant and Marketing Applicant.

All IND and NDA activities undertaken by Marketing Applicant, were carried out with the full and complete permission of Pharmaceutica and Johnson & Johnson. Extension Applicant attaches herewith a

letter dated the 19th day of April, 2001 from Marketing Applicant to Extension Applicant reciting that Extension Applicant is authorized to rely upon the activities of Marketing Applicant before the Regulatory Authority.

Requirements Pursuant to 37 CFR 1.740

37 CFR 1.740(a)(1) A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics.

The approved product is Galantamine hydrobromide (which may also be spelled Galanthamine hydrobromide). Galanthamine is listed in the Merck Index (Twelfth Edition) as compound 4357 (page 736). We enclose a copy of the entry. The Merck Index entry completely identifies Galanthamine. Galanthamine hydrobromide is the acid addition salt of Galanthamine.

37 CFR 1.740(a)(2) A complete identification of the federal statute including the applicable provision of law under which the regulatory review occurred.

The regulatory review occurred pursuant to Section 505 subsections (b) and (i) of the Federal Food, Drug and Cosmetic Act.

37 CFR 1.740(a)(3) An identification of the date on which the product received permission for commercial marketing or use

under the provision of law under which the applicable regulatory review period occurred.

The product received permission for commercial use on the 28th day of February, 2001 (i.e. pursuant to a letter from the FDA to the Marketing Applicant with mailing date of 28th day of February, 2001).

37 CFR 1.740(a)(4) In the case of a drug product, an identification of each active ingredient in the product and as to each active ingredient a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, The Public Health Service Act or the Virus-Serum-Toxin Act or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients) the use of which it was approved, and the provision of law under which it was approved.

The drug product contains a single active ingredient. The single active ingredient is Galantamine hydrobromide (see above). Pursuant to Approval Applicant's approval application the Galantamine hydrobromide was approved for use in the treatment of mild to moderate dementia of the Alzheimer's type. Galanthamine hydrobromide has not previously been approved for any commercial marketing or use under the statutes listed in 37 CFR 1.740(a)(4).

37 CFR 1.740(a)(5) A statement that the application is being submitted within the 60 day period permitted for submission pursuant to 37 CFR 1.720(f) and an indication of the date of the last day on which the application could be submitted.

Pursuant to 37 CFR 1.740~~(a)~~(3) (see above) the product received permission for commercial marketing or use on the 28th day of February, 2001. The 60 day period pursuant to 37 CFR 1.720(f) expires on the 29th day of April, 2001. Therefore, the application is being submitted within the permitted period.

37 CFR 1.740(a)(6) A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue and the date of expiration.

The patent is U.S. Patent Number 4,663,318. The inventor of U.S. '318 is Davis. The issuance date of U.S. '318 is May 5, 1987. The date of expiration of U.S. '318 pursuant to 35 USC Sections 154(a)(2)and 154 (c) is 20 years from the U.S. filing date of January 15, 1986 ***i.e. January 15, 2006***. In this regard please see our calculation set out under paragraph 37 CFR 1.720(g)above.

37 CFR 1.740(a)(7) A copy of the patent for which an extension is being sought including the entire specification (including claims) and drawings.

We enclose a photocopy of U.S. Patent 4,663,318.

37 CFR 1.740(a)(8) A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment or re-examination certificate issued in the patent.

There is no disclaimer. There is no certificate of correction. There is no re-examination certificate issued in the patent. We enclose photocopies of maintenance fee statements for the 'pay year 04' maintenance fee (statement mailed the 16th day of November 1990); for the 'pay year 08' maintenance fee (statement mailed the 5th day of October 1994); and for the 'pay year 12' maintenance fee (statement undated).

37 CFR 1.740(a)(9) A statement that the patent claims the approved product or a method of using or manufacturing the approved product and a showing which lists each applicable patent claim and demonstrates the manner in which at least one such patent claim reads on: ... (ii) The method of using the approved product if the listed claims include any claim to the method of using the improved product.

U.S. Patent 4,663,318 claims a method of using the approved product. The applicable patent claims are claims 1 and 4 in the U.S. '318 patent.

Claim 1 in U.S. Patent 4,663,318 recites:

"1. A method of treating Alzheimer's disease and related dementias which comprises administering to a patient

suffering from such a disease, a therapeutically effective amount of galanthamine or a pharmaceutically acceptable acid addition salt thereof".

The approved product is Galantamine hydrobromide in the tablet dosage form for the treatment of mild to moderate dementias of the Alzheimer's type. Galantamine hydrobromide is the acid addition salt of Galantamine. Therefore, claim 1 in U.S. Patent 4,663,318 reads on a method of using the approved product.

Claim 4 in U.S. Patent 4,663,318 recites:

"A method according to claim 1 where said administration is oral and is in the range 10-2000 mg per day."

The approval is for the tablet. Therefore, claim 4 also reads on a method of using the approved product.

37 CFR 1.740(a)(10) A statement beginning on a new page of the relevant dates and information pursuant to 35 USC 156(g) in order to enable the Secretary of Health and Human Services or the Secretary of Agriculture as appropriate to determine the applicable regulatory view period as follows:
(i) For a patent claiming a human drug, antibiotic or human biological product (A) The effective date of the investigational new drug (IND) application and the IND number; (B) The date on which a new drug application (NDA) or a Product License

Application (PLA) was initially submitted and the NDA or PLA number and (C) The date on which the NDA was approved or the Product License issued.

Please go to new page 13.

Application for approval of the approved product was submitted under Investigational New Drug Application Number 51,538 having effective date October 4, 1996. Application for approval of the approved product was submitted under New Drug application (NDA) number NDA 21-169 which was initially submitted on the 29th day of September,1999. As set out in regard to 37 CFR 1.740(a)(3) (see above) NDA 21-169 was approved on the 28th day of February, 2001. (copy enclosed)

37 CFR 1.740(a)(11) A brief description beginning on a new page of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities.

Please go to new page 15.

Relevant Activities under IND 51,538

Date	Serial Number	From	Type	Details
9/5/1996	000	Janssen	Original IND	Original Investigational New Drug Application for REMINYL Tablets.
9/12/1996		FDA	Correspondence	Acknowledgement of receipt of the IND.
9/18/1996		FDA	Correspondence	Request CMC information
9/27/1996	001	Janssen	Information Amendment	Response to 9/18/1996 CMC information request.
10/4/1996		FDA	Phone	Initiation of Phase III study.
10/17/1996			FDA Meeting	End-of-Phase II meeting held for REMINYL Tablets.
12/2/1996	006	Janssen	Information Amendment	Submission of pharmacology/toxicology and clinical reports: N123642, N123643, and N121951.
3/12/1997		FDA	Correspondence	FDA comments and requests regarding IND 51,538.
3/26/1997	013	Janssen	General Correspondence	Initial response to FDA letter of 3/12/1997.
4/1/1997			FDA Meeting	Pre-NDA CMC Meeting held with FDA for REMINYL Tablets.
4/7/1997	014	Janssen	Protocol Amendment	Submission of New Protocol GAL-INT-2.
5/8/1997	016	Janssen	Response to FDA Request for Information	Response to FDA correspondence dated 3/12/1997.
7/23/1997	020	Janssen	Protocol Amendment	Submission of New Protocol GAL-USA-3.
8/15/1997	021	Janssen	Protocol Amendment	Submission of New Protocol GAL-USA-2.
8/21/1997	022	Janssen	Information Amendment	Submission of Janssen's proposal for conducting carcinogenicity bioassays for galantamine.
11/25/1997		FDA	Fax	Comments on carcinogenicity proposal submitted on 8/21/1997.
11/26/1997	031	Janssen	Protocol Amendment	Submission of New Protocol GAL-USA-5.
12/18/1997	033	Janssen	Information Amendment	Addendum to Janssen's proposal for carcinogenicity testing program submitted on 8/21/1997 in response to FDA comments of 11/25/1997.
2/4/1998	038	Janssen	Protocol Amendment	Submission of New Protocols GAL-USA-6 and GAL-USA-9.
3/5/1998		FDA	Correspondence	FDA comments on carcinogenicity proposal submitted on 12/18/1997.
4/20/1998	051	Janssen	Information Amendment	Submission of revised Investigator's Brochure in response to FDA correspondence of 3/12/1997.
5/8/1998	056	Janssen	Information Amendment	Submission of the following nonclinical study reports: N125607, N123841, N121459, N123701, and N123873.
7/2/1998	059	Janssen	Draft Protocol	Submission of Draft Protocol GAL-USA-10 and request for FDA comments.
7/29/1998		FDA	Correspondence	Comments on draft protocol (GAL-USA-10) submission of 7/2/1998.
8/20/1998	061	Janssen	Protocol Amendment	Submission of New Protocol GAL-USA-10.
10/9/1998		FDA	Phone	Information request from FDA Biopharmaceutics Reviewer.
10/13/1998			FDA Meeting	Pre-NDA Meeting held with FDA for REMINYL Tablets.

Date	Serial Number	From	Type	Details
10/23/1998	067	Janssen	Response to FDA Request for Information	Submission of information on galantamine metabolism in human, formulation links, and draft dissolution data in response to FDA request of 10/9/1998.
12/9/1998	074	Janssen	Information Amendment	Submission of the following toxicity studies: N130862, N130784, N137003, N130719, N130813, and N133672.
12/28/1998	076	Janssen	Information Amendment	Submission of the following toxicity studies: N137047 and N137048.
1/29/1999	083	Janssen	Correspondence	Submission of information regarding carcinogenicity assays for 2/3/1999 FDA teleconference.
2/3/1999			Teleconference	Galantamine carcinogenicity teleconference held with FDA.
2/4/1999	084	Janssen	General Correspondence	Type-A Meeting Request for REMINYL Tablets.
3/5/1999	092	Janssen	Protocol Amendment	Submission of New Protocol GAL-USA-11.
3/10/1999	093	Janssen	General Correspondence	Submission of Type-A Meeting (3/24/1999) pre-meeting package.
3/24/1999			FDA Meeting	Type-A Meeting held with FDA.
4/13/1999	102	Janssen	General Correspondence	Meeting request to discuss the natural to synthetic switch for galantamine.
4/22/1999	104	Janssen	Protocol Amendment	Submission of New Protocol GAL-USA-12.
5/6/1999		FDA	Correspondence	FDA comments on new protocol (GAL-USA-11) submission of 3/5/1999.
5/10/1999	108	Janssen	Protocol Amendment	Submission of New Protocol GAL-USA-16.
5/26/1999	112	Janssen	Information Amendment	Submission of the following toxicity studies: N133946, N133935, and N137197.
5/28/1999	113	Janssen	General Correspondence	Submission of meeting package for 6/16/1999 FDA meeting to discuss synthetic galantamine.
6/16/1999			FDA meeting	FDA meeting held to discuss synthetic galantamine.
6/28/1999	120	Janssen	Protocol Amendment	Submission of New Protocol GAL-USA-17.
6/30/1999	121	Janssen	General Correspondence	Response to FDA comments of 5/6/1999 regarding design of protocol GAL-USA-11.
7/2/1999	122	Janssen	Information Amendment	Submission of information amendment consisting of the Clinical Expert Report and Clinical Summary from the REMINYL International Registration File (N137430 and N137396).
7/26/1999	130	Janssen	General Correspondence	Provision of sample E-submission materials.
9/17/1999	144	Janssen	Information Amendment	Submission of CMC information amendment supporting the use of synthetic galantamine.
3/15/2000	165	Janssen	Protocol Amendment	Submission of New Protocol GAL-USA-18.
4/14/2000	170	Janssen	Response to FDA Request for Information	Identification of Norgalantamine structure.
6/14/2000			FDA Meeting	Type-B Meeting held with FDA.
7/7/2000	177	Janssen	Protocol Amendment	Submission of New Protocol GAL-USA-19.

Relevant Activities under NDA 21-169

Date	From	Type	Details
9/29/1999	Janssen	Original NDA	Original New Drug Application for REMINYL Tablets.
10/20/1999	FDA	Correspondence	Acknowledgement of receipt of the NDA.
11/1/1999	Janssen	Correspondence	Letter to authorize FDA to review galantamine DMF.
11/12/1999	Janssen	Amendment	Response to CMC information request of 11/1/1999.
11/23/1999	Janssen	Correspondence	Submission of adverse event information for GAL-USA-1, GAL-INT-1, and GAL-INT-2, per FDA request of 11/4/1999.
1/12/2000	FDA	Phone	Request from a Medical Reviewer for information pertaining to studies GAL-INT-1 and GAL-USA-1.
1/18/2000	FDA	Phone	Request from a Statistician for statistical programming information for studies GAL-USA-1, GAL-INT-1, GAL-INT-2 and 95-05.
1/21/2000	Janssen	Correspondence	Submission of information pertaining to studies GAL-INT-1 and GAL-USA-1 per FDA request of 1/12/2000.
1/27/2000	Janssen	Amendment	Submission of statistical programming information from studies GAL-USA-1, GAL-INT-1, GAL-INT-2, and 95-05, per FDA request of 1/18/2000.
2/8/2000	Janssen	Correspondence	Response to FDA request for information pertaining to PK Report N137314 on 2/3/2000.
2/18/2000	Janssen	Correspondence	Response to FDA request for information pertaining to PK Report N141967 on 2/18/2000; Submission of galantamine tablets dissolution data per FDA request of 2/8/2000.
2/25/2000	Janssen	Correspondence	Submission of galantamine tablets dissolution data from Lot 0150L following submission of 2/18/2000.
2/25/2000	Janssen	Amendment	Submission of additional safety and efficacy information for REMINYL Tablets.
3/21/2000	FDA	Information Request Letter	Request for CMC information pertaining to NDA 21-169.
4/10/2000	FDA	Phone	Divisional comments on potential approval timeframe; Use of MEDRA system for analyzing AEs; Fast track review for Lewy-Body Dementia indication.
4/18/2000	Janssen	Correspondence	Response to request for information of 4/18/2000.
4/19/2000	FDA	Fax	Receipt of FDA consultation response regarding acceptability of REMINYL trade name.
4/20/2000	Janssen	Amendment	Response to information request from a Medical Reviewer on 4/11/2000.
5/23/2000	Janssen	Phone	Potential nature/timing of action letter for REMINYL NDA.
5/25/2000	Janssen	Amendment	Response to FDA Information Request Letter (CMC) dated 3/21/2000.
6/8/2000	Janssen	Amendment	Response to information request from a Pharmacology/Toxicology Reviewer on 5/3/2000.
6/29/2000	FDA	Information Request Letter	Request for CMC information pertaining to NDA 21-169.
7/19/2000	Janssen	Amendment	Response to FDA Information Request Letter (CMC) dated 6/29/2000.
7/29/2000	FDA	Action Letter	FDA Approvable Action Letter for REMINYL Tablets.
8/3/2000	Janssen	Correspondence	Intention to file an amendment to 7/29/2000 Approvable Letter.
8/9/2000	FDA	Phone	Scheduling of teleconference to discuss FDA labeling modifications.

Date	From	Type	Details
8/15/2000		Teleconference	Teleconference held to discuss FDA's modifications to REMINYL labeling.
8/31/2000	Janssen	Amendment	Resubmission in response to 7/29/2000 Approvable Letter.
9/22/2000	FDA	Correspondence	Acknowledgement of receipt of 8/31/2000 resubmission (Assignment of Class 2 review status).
9/27/2000	Janssen	Correspondence	Appeal of FDA Classification of 8/31/2000 resubmission.
10/2/2000	Janssen	Amendment	Submission of adverse event information from study GAL-USA-11, per FDA request of 10/2/2000 from a Medical Reviewer.
10/12/2000	Janssen	Amendment	Response to information request from a Medical Reviewer on 10/2/2000.
12/01/2000	Janssen	Amendment	Response to information requests from a Medical Reviewer on 11/7/2000 and 11/8/2000.
12/5/2000	Janssen	Amendment	Response to information request from a Medical Reviewer on 11/14/2000.
1/17/2001	Janssen	Amendment	Response to information request from a Medical Reviewer on 12/18/2000.
1/18/2001	Janssen	Amendment	Response to information request from a Medical Reviewer on 1/8/2001.
1/23/2001	Janssen	Amendment	Response to information request from a Medical Reviewer on 1/12/2001.
1/30/2001	Janssen	Amendment	Response to information request from a Medical Reviewer on 1/23/2001.
2/6/2001	Janssen	Amendment	Submission of revised package labeling for REMINYL Tablets.
2/12/2001		Teleconference	Teleconference held to discuss final product labeling for REMINYL Tablets.
2/23/2001	Janssen	Fax	Request to DDMAC for comments regarding a proposed press release for REMINYL Tablets.
2/27/2001	FDA	Fax	DDMAC comments regarding proposed press release for REMINYL Tablets submitted 2/23/2001.
2/28/2001	FDA	Action Letter	Approval Letter for REMINYL Tablets.
3/20/2001	Janssen	Amendment	Submission of Final Printed Labeling (FPL) for approved NDA 21-169.

37 CFR 1.740(a)(12) A statement beginning on a new page that in the opinion of the applicant the patent is eligible for extension and a statement as to the length of extension claimed including how the length of extension was determined.

Please go to new page 20.

Extension Applicant in its opinion is eligible for the requested extension of patent term. We are required to show our calculation of the length of extension claimed which is set out below.

Calculation of patent term extension for a human drug, antibiotic drug, or human biological product pursuant to 37 CFR 1.775.

37 CFR 1.775(c) - the length of the regulatory review period ... is the sum of:

(1) The number of days in the period beginning on the date an exemption under subsection (i) of Section 505 of the Federal Food, Drug and Cosmetic Act became effective for the approved product and ending on the date the application was initially submitted for such product under those sections or under Section 351 of the Public Health Service Act.

The length of the regulatory review period ... is the sum of ... [37 CFR 1.775(c)(1)] (see above) and

(2) The number of days in the period beginning on the date the application was initially submitted for the approved product under .... subsection (b) of Section 505 ... of the Federal Food, Drug and Cosmetic Act and ending on the date such application was approved under such section.

The effective date of the IND permission

under the provisions of Section 505(i) of the FFDCA was October 4, 1996. The NDA application under the provisions of Section 505(b) of the FFDCA was initially submitted on September 29, 1999. Thus, the number of days in the period beginning on the date an exemption under Section 505(i) of the FFDCA and ending on the date of the NDA was initially submitted (under Section 505(b) FFDCA) is 1089 days.

The NDA was initially submitted (under Section 505(b) of the FFDCA) on September 29, 1999. The application was approved under such section on February 28, 2001. The number of days in the period beginning on the date the application was initially submitted and ending on the date such application was approved is 518 days.

We calculate the length of the regulatory review period (to be determined by the Secretary of Health and Human Services) to be 1607 days (subject to an reductions pursuant to paragraphs (d)(1)(i) through (d)(1)(iii).

U.S. Patent 4,663,318 issued on May 5, 1987. Since there are no days in the periods of paragraphs (c)(1) and (c)(2) of 37 CFR 1.775 which were on or before the date on which the patent issued then there are no deductions under 37 CFR 1.775(d)(1)(i).

Extension Applicant is a small company. Small companies often rely on Licensees in order to secure marketing approval. Licensing arrangements take time. We believe that the record shows that there has been no lack of diligence. We believe there should be no deduction under 37 CFR 1.775(d)(1)(ii).

The deduction under 37 CFR 1.775(d)(1)(iii) is 544 days. Therefore, the extension under 37 CFR 1.775(d)(1) is 1063 days.

37 CFR 1.775(d)(2). As set out under 37 CFR 1.740(a)(6) (see above) the original term of the patent ends on January 15, 2006. Adding the number of days determined in paragraph (d)(1) of this section gives the 12th day of December, 2008.

37 CFR 1.775(d)(3). Adding 14 years to the date of approval of the application under ... subection (b) of Section 505 ... of the Federal Food, Drug and Cosmetic Act gives the 28th day of February, 2015.

37 CFR 1.775(d)(4). Selecting the earlier date of the dates for the ends of the periods obtained pursuant to paragraphs (d)(2) and (d)(3) (see above) gives the 12th day of December, 2008.

37 CFR 1.775(d)(5). Since the original patent was issued after September 24, 1984 (i.e. on May 5, 1987) then (pursuant to 37 CFR 1.775(d)(5)(i)) add five years to January 15, 2006 (the original expiration date) gives January 15, 2011.

Pursuant to 37 CFR 1.775(d)(5)(ii) select the earlier date from the dates obtained pursuant to paragraphs (d)(4) and (d)(5)(i) of 37 CFR 1.775 gives the 12th day of December, 2008.

It follows from the above calculation that the 14 year patent term limit(i.e. the limit of 35 USC 156(c)(3)) does not apply. Also the 2 or 3 year patent term extension limits of 35 USC 156(g)(6)(C) do not apply.

37 CFR 1.740(a)(13) A statement that applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought.

Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought.

37 CFR 1.740(a)(14) The prescribed fee for receiving and acting upon the application for extension (see section 1.20(j)).

Pursuant to 37 CFR 1.20(j)(1) the fee for extension of patent term for financial year 2001 is $1,120.00. We enclose our check.

In the event we have under paid/ over paid the required fee the office is hereby authorized to suitably debit/credit our Deposit Account Number 12-0425.

37 CFR 1.740(a)(15) The name, address, and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed.

Please direct inquiries and correspondence relating to this application for patent term extension to:

John Richards, Esq.
Ladas & Parry
26 West 61 Street
New York, New York 10023
Telephone Number (212) 708-1915
Fax Numbers (212) 246-8959 and
(212) 246-8925

37 CFR 1.740(b) The application under this section must be accompanied by two additional copies of such application (for a total of three copies).

We enclose the required three copies.

Respectfully submitted,

JOHN RICHARDS
Ladas & Parry
26 West 61st Street
New York, N.Y. 10023
Telephone No. (212) 708-1915
Registration No. 31053

Enclosure list

Copy approval letter dated February 28, 2001 from the Food and Drug Administration to Janssen Research Foundation

Statement Under 37 CFR 3.73(b)

Power of Attorney

Copy letter dated April 19, 2001 from Janssen Research Foundation to Dr. Bonnie Davis

Page 736 The Merck Index

Soft copy U.S. Patent Number 4,663,318

3 Maintenance Fee Statements

DEPARTMENT OF HEA_H & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-169

Janssen Research Foundation
Attention: Charles LaPree
Assitant Director, Regulatory Affairs
1125 Trenton-Harbourton Road
P.O. Box 200
Titusville, NJ 08560-0200

Dear Mr. LaPree:

Please refer to your new drug application (NDA) dated September 29, 1999, received September 29, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Reminyl® (galantamine hydrobromide) Tablets.

We acknowledge receipt of your submissions dated:

August 3, 2000	October 2, 2000	December 5, 2000	January 23, 2001
August 31, 2000	October 12, 2000	January 17, 2001	January 30, 2001
September 12, 2000	December 1, 2000	January 18, 2001	February 6, 2001

Your submission of August 31, 2000 constituted a complete response to our July 29, 2000 approvable action letter.

This new drug application provides for the use of Reminyl® (galantamine hydrobromide) Tablets for the treatment of mild to moderate dementia of the Alzheimer's type.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format*-NDAs (January 1999).

For administrative purposes, this submission should be designated "FPL for approved NDA 21-169." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your Phase 4 commitment specified in your submission dated August 31, 2001, to provide the histopathological examinations on cervices of all animals in the rat carcinogenicity study.

Reference is made to your correspondence submitted within this NDA, requesting a waiver for pediatric studies under 21 CFR 314.55(c).

We have reviewed the information you have submitted and agree that a waiver is justified for Reminyl® for the treatment of mild to moderate dementia of the Alzheimer's type for the pediatric population.

Accordingly, a waiver for pediatric studies for this application is granted under 21 CFR 314.55 at this time.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Neuropharmacological Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Melina Fanari, R. Ph, Regulatory Management Officer, at (301) 594-5526.

Sincerely,

(See appended electronic signature page)

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

/s/
Robert Temple
2/28/01 03:31:16 PM

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D. C. 20231

PAYOR NUMBER
000140

75M7/1005

LADAS & PARRY
26 WEST 61ST STREET
NEW YORK, NY 10023

DATE MAILED
10/05/94

MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 10, "status" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 10, "status" below. An explanation of the codes appears on the reverse of the Maintenance Fee Statement. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITM NBR	PATENT NUMBER	FEE CDE	FEE AMOUNT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	4,663,318	184	1870	----	06/819,141	05/05/87	01/15/86	08	NO	PAID

If the "status" column for a patent number listed above does not indicate "PAID" a code or an asterisk (*) will appear in the "status" column. Where an asterisk (*) appears, the codes are set out below by the related item number. An explanation of the codes indicated in the "status" column and as set out below by the related item number appears on the reverse of the maintenance fee statement.

ET 728212517 US

ITM NBR	ATTY DKT NUMBER
1	U 5631

DIRECT THE RESPONSE TOGETHER WITH ANY QUESTIONS ABOUT THIS NOTICE TO:
COMMISSIONER OF PATENTS AND TRADEMARKS, BOX M. FEE, WASHINGTON, DC 20231

Practitioner's Docket No. NPSP 010231 (HW) ***PATENT***

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:
Application No.: Group No.:
Filed: Examiner:
For:

Patent No.* : 4,663,318 Issue Date: May 5, 1987
Title: Method of Treating Alzheimer's Disease.
Inventor: Bonnie Davis.
Reexamination No.: _____ Issue Date: _____
Reissue: _____ Issue Date: _____
**NOTE: Insert name(s) of inventor(s) and title for patent.*

Assistant Commissioner for Patents
Washington, D.C. 20231

STATEMENT UNDER 37 C.F.R. § 3.73(b) ESTABLISHING RIGHT OF ASSIGNEE TO TAKE ACTION

NOTE: 37 CFR 3.73(b) states: "When an assignee seeks to take action in a matter before the Office with respect to a patent application, ..., patent, registration, or reexamination proceeding, the assignee must establish its ownership of the property to the satisfaction of the Commissioner. Ownership is established by submitting to the Office, in the Office file related to the matter in which action is sought to be taken, documentary evidence of a chain of title from the original owner to the assignee (e.g., copy of an executed assignment submitted for recording) or by specifying (e.g., reel and frame number) where such evidence is recorded in the Office. The submission establishing ownership must be signed by a party authorized to act on behalf of the assignee. Documents submitted to establish ownership may be required to be recorded as a condition to permitting the assignee to take action in a matter pending before the Office."

CERTIFICATION UNDER 37 C.F.R. 1.8(a) and 1.10*
(When using Express Mail, the Express Mail label number is mandatory; Express Mail certification is optional.)

I hereby certify that, on the date shown below, this correspondence is being:

MAILING

☒ deposited with the United States Postal Service in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

37 C.F.R. 1.8(a)

with sufficient postage as first class mail.

37 C.F.R. 1.10*

(x) as "Express Mail Post Office to Address" Mailing Label No. EL 728212517US (mandatory)

TRANSMISSION

☐ transmitted by facsimile to the Patent and Trademark Office.

Date: April 24, 2001

Maria Melian
Signature

Maria Melian
(type or print name of person certifying)

***WARNING:** Each paper or fee filed by "Express Mail" must have the number of the "Express Mail" mailing label placed thereon prior to mailing. 37 C.F.R. 1.10(b).*
"Since the filing of correspondence under § 1.10 without the Express Mail mailing label thereon is an oversight that can be avoided by the exercise of reasonable care, requests for waiver of this requirement will not be granted on petition." Notice of Oct. 24, 1996, 60 Fed. Reg. 56,439, at 56,442.

EL 728212517 US

NOTE: "Section 3.73(b) is amended to remove the sentence requiring an assignee to specifically state that the evidentiary documents have been reviewed and to certify that title is in the assignee seeking to take action. The sentence is deemed to be unnecessary in view of the amendment to §§ 1.4(d) and 10.18." Notice of Oct. 10, 1997, 62 Fed. Reg. 53,131, at 53,174.

1. The assignee(s) of the entire right, title and interest hereby seek(s) to take action in the PTO in this matter.

IDENTIFICATION OF ASSIGNEE

2. SYNAPTECH INC , of c/o Schwartz & Salomon, 225 Broadway, 42nd Fl, NewYork , NY 10007-3001

Name of assignee

Corporation

Type of assignee, e.g., corporation, partnership, university, government agency, etc.

NOTE: The Notice of April 30, 1993 (1150 O.G. 62-64) points out:

"The statement under 37 CFR 3.73(b) may be signed on behalf of the assignee in the following two manners if the assignee is an organization (e.g., corporation, partnership, university, government agency, etc.).

"(1) The statement may be signed by a person in the organization having apparent authority to sign on behalf of the organization. An officer (president, vice-president, secretary, or treasurer) is presumed to have authority to sign on behalf of the organization. The signature of the chairman of the board of directors is acceptable, but not the signature of an individual director. A person having a title (manager, director, administrator, general counsel) that does not clearly set forth that person as an officer of the assignee is not presumed to be an officer of the assignee or to have authority to sign the statement on behalf of the assignee. A power of attorney from the inventors in an organization to a practitioner to prosecute a patent application does not make the practitioner an official of an assignee or empower the practitioner to sign the statement on behalf of the assignee.

"(2) The statement may be signed by any person, if the statement includes an averment that the person is empowered to sign the statement on behalf of the assignee and, if not signed by a registered practitioner, the statement must be in oath or declaration form. Where a statement does not include such an averment, and the person signing does not hold a position in the organization that would give rise to a presumption that the person is empowered to sign the statement on behalf of the assignee, evidence of the person's authority to sign will be required."

(complete the following, if applicable)

(X) I, the person signing below, state that I am empowered to sign this statement on behalf of the assignee.I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

BASIS OF ASSIGNEE'S INTEREST

Ownership by the assignee is established as follows:

A.

1. ☐ An assignment from the inventor(s) of the matter identified above, which

was recorded in the PTO at
Reel____ Frame____

Practitioner's Docket No. NPSP 010231(HW)
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

☐ In re application of:
Application No.: Group No.:
Filed: Examiner:
For:

(X) Patent No.*: 4,663,318 Issued: May 5, 1987
Title: Method of treating Alzheimer's disease.
Inventor: Bonnie Davis.

**NOTE: Insert name(s) of all inventor(s) and title also for patent.*

Assistant Commissioner for Patents
Washington, D.C. 20231

POWER OF ATTORNEY BY ASSIGNEE OF ENTIRE INTEREST
(REVOCATION OF PRIOR POWERS)

As assignee of record of the entire interest of the above identified

☐ application,

(X) patent,

REVOCATION OF PRIOR POWERS OF ATTORNEY

all powers of attorney previously given are hereby revoked and

NEW POWER OF ATTORNEY

the following attorney(s) and/or agent(s) are hereby appointed to prosecute and transact all business in the Patent and Trademark Office connected therewith.

JOSEPH H. HANDELMAN, 26179	JULIAN H. COHEN, 20302
JOHN RICHARDS, 31053	WILLIAM R. EVANS 25858
RICHARD J. STREIT, 25765	JANET I. CORD, 33778
PETER D. GALLOWAY, 27885	CLIFFORD J. MASS, 30086
IAIN C. BAILLIE, 24090	CYNTHIA R. MILLER, 34678
RICHARD P. BERG, 28145	

EL 728212517 US

SEND CORRESPONDENCE TO:

Ladas & Parry
26 West 61st Street
New York, N.Y. 10023

DIRECT TELEPHONE CALLS TO:
(Name and telephone number)

(212) 708-1915

Optional Customer No. Bar Code

00140
00140
PATENT TRADEMARK OFFICE

Synaptech Inc
(type or print identity of assignee of entire interest)

c/o Schwartz and Salomon, 225 Broadway, 42nd Fl.
Address

New York, N.Y. 10007-3001

(X) Recorded in PTO on 02/12/96
Reel 8376
Frame 0943

☐ Recorded herewith

ASSIGNEE STATEMENT

Attached to this power is a "STATEMENT UNDER 37 C.F.R. section 3.73(b)."

(X) Bonnie Davis
Signature

Date: THIS 6th DAY OF APRIL 2001

(X) BONNIE DAVIS M.D.
(type or print name of person authorized to sign on behalf of assignee)

(X) SCIENTIFIC DIRECTOR.
Title

NOTE: The assignee of the entire interest may revoke previous powers and be represented by an attorney of his or her selection. 37 C.F.R. 1.36.

(check the following item, if it forms a part of this power of attorney)

☐ Added page—Authorization of attorney(s) to accept and follow instructions from representative.

2. ☐ An assignment (document) separately being submitted for recordal herewith.

AND/OR

B. (x) A chain of title from the inventor(s) to the current assignee as shown below:

1. From: Bonnie Davis
Name of inventor(s)
To: Intelligen Corporation of P.O. Box 157, Cold Spring Harbor, New York, 11724
Recorded in PTO: Reel 5392, Frame 428—430

2. From: Intelligen Corporation (address as above)
Name of inventor(s) or assignee
To: Synaptech Inc. c/o Schwartz & Saloman, 225 Broadway, 42nd Floor, New York, NY 10007-3001
Recorded in PTO: Reel 8376, Frame 0935-0943

3. From: _____
Name of inventor(s) or assignee
To: _____
Recorded in PTO: Reel _____, Frame _____

(check item below, and add details, if applicable)

☐ Additional documents in the chain of title are listed in the attached Supplemental Sheet.

COPIES OF DOCUMENTS IN CHAIN OF TITLE

(complete this item, if copies are being sent)

☒ Copies of the assignment(s) or other document(s) in the chain of title are attached as follows:

☐	A	☐	1	☐	2		
(x)	B	(x)	1	(x)	2	☐	3

(X) April 6th 2001
date

Bonnie Davis
Signature of authorized person

Bonnie Davis M.D.
(type or print name of authorized person)

Scientific Director
Title of authorized person

Reg. No.:

Tel. No.: ( )

Customer No.:

SIGNATURE OF PRACTITIONER

(type or print name of practitioner)

P.O. Address

c/o Ladas & Parry
26 West 61st Street
New York, N.Y. 10023

8-10-518 US631

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

☐ In re application of*: Bonnie Davis
Serial No.: 06/819,141 Group No. 125
Filed: May 15, 1986 Examiner: Friedman
For*: METHOD OF TREATING ALZHEIMER'S DISEASE

☒ Patent: 4,663,318 Issued: May 5, 1987

*NOTE: Insert name(s) of inventor(s) and title also for patent. Where recordal is with respect to a maintenance fee payment also insert application serial number and filing date and add Box M. Fee to Express

Commissioner of Patents and Trademarks
Washington, D.C. 20231

RECORDAL OF ASSIGNMENT (37 CFR 1.331)

1. Kindly record the enclosed assignment for the above identified
   ☐ application
   ☒ patent
2. When recordal has been effected, please return the original assignment document to the undersigned.
3. Fee Payment (37 CFR 1.21(h))
   ☒ Attached is a check in the sum of $8.00.
   ☐ Charge Account No. _____ the sum of $8.00. A duplicate of this recordal request is attached.

NOTE: 37 CFR 1.21(h). For recording each assignment, agreement or other paper relating to the property in a patent or application, per property, $8.00.

MS392 mail 28

Tel. No. ( )
JOHN RICHARDS
Reg. No. c/o LADAS & PARRY
26 WEST 61st STREET
NEW YORK, N.Y. 10023
Reg. No. 31053 (212) 708-1915

SIGNATURE OF ATTORNEY

Type or print name of attorney

P.O. Address

CERTIFICATE OF MAILING (37 CFR 1.8a)

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to the: Commissioner of Patents and Trademarks, Washington, D.C. 20231.

JOHN RICHARDS
(Type or print name of person mailing paper)

Date 1 August 90

(Signature of person mailing paper)

91520292

(Recordal of Assignment (10-83)

120 TL 08/13/90 06819141 1 518 8.00 CK

U 5631

PATENT

For: ☐ U.S. and/or ☐ Foreign Rights
For: ☐ U.S. Application or ☐ U.S. Patent
By: ☐ Inventor(s) or ☐ Present Owner

ASSIGNMENT OF INVENTION

In consideration of the payment by ASSIGNEE to ASSIGNOR of the sum of One Dollar ($1.00), the receipt of which is hereby acknowledged, and for other good and valuable consideration,

ASSIGNOR: (inventor(s) or person(s) or entity(ies) who own the invention)

Bonnie DAVIS
(Type or print name(s) of ASSIGNOR(S))
17 SEACREST DRIVE
Address
HUNTINGTON, NEW YORK 11743

U.S.S.A.
Nationality

(If assignment is by person or entity to whom invention was previously assigned and this was recorded in PTO add the following)

Recorded on _____
Reel _____
Frame _____

hereby sells, assigns and transfers to ASSIGNEE:

INTELLIGEN CORPORATION
(Type or print name of ASSIGNEE)
P.O. Box 157
Address
COLD SPRING HALBOR NEW YORK 11724

Nationality

and the successors, assigns and legal representatives of the ASSIGNEE

(complete one of the following)

☒ the entire right, title and interest
☐ an undivided _____ percent (_____%) interest

for the United States and its territorial possessions

(check the following box if foreign rights are also to be assigned)

☐ and in all foreign countries, including all rights to claim priority,

in and to any and all improvements which are disclosed in the invention entitled:
METHOD OF TREATING ALZHEIMER'S DESEASE

(check and complete (a), (b), (c) or (d))

and which is found in

RECORDED
PATENT AND TRADEMARK
OFFICE

AUG - 3 1990

(a) ☐ U.S. patent application executed on even date herewith

(b) ☐ U.S. patent application executed on _____

(c) ☐ U.S. application serial no. 0 /_____ filed on _____

(d) ☒ U.S. patent no. 4,663,318 issued MAY 5, 1987

(also check (a) if foreign application(s) is also being assigned)

(e) ☐ and any legal equivalent thereof in a foreign country, including the right to claim priority

and, in and to, all Letters Patent to be obtained for said invention by the above application or any continuation, division, renewal, or substitute thereof, and as to letters patent any re-issue or re-examination thereof.

ASSIGNOR hereby covenants that no assignment, sale, agreement or encumbrance has been or will be made or entered into which would conflict with this assignment.

ASSIGNOR further covenants that ASSIGNEE will, upon its request, be provided promptly with all pertinent facts and documents relating to said invention and said Letters Patent and legal equivalents as may be known and accessible to ASSIGNOR and will testify as to the same in any interference, litigation or proceeding related thereto and will promptly execute and deliver to ASSIGNEE or its legal representatives any and all papers, instruments or affidavits required to apply for, obtain, maintain, issue and enforce said application, said invention and said Letters Patent and said equivalents thereof which may be necessary or desirable to carry out the purposes thereof.

IN WITNESS WHEREOF, I/We have hereunto set hand and seal this July 26, 1990 (Date of signing).

WARNING: *Date of signing must be the same as the date of execution of the application if item (a) was checked above.*

X Bonnie W Davis

Signature of ASSIGNOR(S) Bonnie DAVIS

If ASSIGNOR is a legal entity complete the following information

_____

Type or print the name of the above person authorized to sign on behalf of ASSIGNOR

_____

Title

NOTE: No witnessing, acknowledgment or legalization is necessary. If the assignment is executed or legalized then it will only be prima facie evidence of execution 35 USC 261. Use next page if acknowledgment is desired.

☐ Notarization or Legalization Page Added.

(Assignment of Invention [16-3]—page 2 of 2)

RECORDED: 08/03/1990

REEL 005392 FRAME 130

07-17-1996

100233540

Attorney's Docket No. U 3031-0 SPU 4295

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Box Assignments
Commissioner of Patents and Trademarks
Washington, D.C. 20231

NOTE: "Documents and cover sheets to be recorded should be addressed to Commissioner of Patents and Trademarks, Box Assignments, Washington, D.C. 20231, unless they are filed together with new applications or with a petition under § 3.81(b)." 37 CFR 3.27.

ASSIGNMENT (DOCUMENT) COVER SHEET (37 CFR 3.31)

NOTE: "A cover sheet may not refer to both patents and trademarks." 37 CFR 3.31(g).

Attached please find an assignment (document) for recordal.

CERTIFICATION 37 CFR 1.8(a) and 1.10

I hereby certify that this correspondence is, on the date shown below, being:

MAILING

☒ deposited with the United States Postal Service in an envelope addressed to the Commissioner of Patents and Trademarks, Washington, D.C. 20231.

37 CFR 1.8(a)

☒ with sufficient postage as first class mail.

37 CFR 1.10

☐ as "Express Mail Post Office to Addressee" Mailing Label No. _____

TRANSMISSION

☐ transmitted by facsimile to the Patent and Trademark Office.

_____
Signature

Date: February 8, 1996

John Richards
(type or print name of person certifying)

(Assignment (Document) Cover Sheet [16-6] —page 1 of 6)

IDENTIFICATION OF APPLICATION(S) AND/OR PATENT(S) FOR ASSIGNMENT (DOCUMENT) RECORDAL (37 CFR 3.21 and 37 CFR 3.31(a)(4))

NOTE: "An assignment relating to a patent must identify the patent by the patent number. An assignment relating to a national patent application must identify the national patent application by the application number (consisting of the series code and the serial number, e.g., 07/123,456) or the serial number and the filing date. An assignment relating to an international patent application which designates the United States of America must identify the international application by the international application number (e.g., PCT/US90/01234)." 37 CFR 3.21.

NOTE: § 3.21 does not apply to documents other than assignments. Notice of June 24, 1992 (1140 O.G. 63-72 at 67).

1. This assignment is for the following patent application and/or issued patent:

National application: SN: 0 / 819,141 filed on January 15, 1986

Provisional application: / filed on

International application: PCT/ /

Patent No: 4,663,318 issued: May 5, 1987

(complete if applicable) which was previously assigned and recorded

Date _____ Reel _____

Frame _____

(also complete the following, if applicable)

☐ and also for the applications and/or patents shown on the attached list of FURTHER APPLICATION(S) and/or PATENT(S) BEING ASSIGNED

Number of pages added _____

NOTE: "Where there is a listing of properties contained within a document, any listing may be copied and attached to the cover sheet to reduce the amount of typing necessary. A notation of this attachment can be made in lieu of entering every property identification number on the cover sheet. Notice of June 24, 1992 (1140 O.G. 63-72 at 67).

TOTAL NUMBER OF APPLICATIONS AND/OR PATENTS AND TOTAL FEE (37 CFR 3.28(a)(4))

2. A. The total number of applications and/or patents identified in this cover sheet is

1

B. The total fee is (37 CFR 1.21(h)):

1 (Total number of applications and/or patents) × $40.00 = $ 40.00

C. Payment of fee is made by:

☒ the attached check for $ 40.00

☐ Please charge Account _____

the sum of $ _____

A duplicate of this cover sheet is attached.

Please charge Account 12-0425 for any fee deficiency or credit to account any overpayment.

NAME OF PARTY(IES) CONVEYING INTEREST (37 CFR 3.31(a)(1))

NOTE: "The term 'party' as used in this rule [§ 3.31] means the person whose name appears on the documents to be recorded, that person's attorney or registered agent, or a corporate officer where a corporation's name appears on the documents." Notice of June 24, 1992 (1140 O.G. 53-72, at 55).

3. The party(ies) conveying interest is (are):

Name 1: Intelligen Corporation

Name 2:

Name 3:

NAME AND ADDRESS OF PARTY(IES) RECEIVING INTEREST (37 CFR 3.31(a)(2))

4. The rights are being conveyed to:

Name: Synaptech Inc.

Address: c/o Schwartz & Salomon
225 Broadway, 42nd Floor
New York, NY 10007-3001

DESCRIPTION OF INTEREST CONVEYED OR TRANSACTION RECORDED (37 CFR 3.31(a)(3))

5. The accompanying document intends to accomplish:

- [x] an assignment.
- [ ] a security agreement.
- [ ] a merger.
- [ ] a license
- [ ] a change of name.
- [ ] a change of address.
- [ ] other:

NAME AND ADDRESS OF PARTY TO WHOM CORRESPONDENCE SHOULD BE MAILED (37 CFR 3.31(a)(5))

6. Please address correspondence to:

Name: John Richards c/o Ladas & Parry
Address: 26 West 61 Street
New York, NY 10023
Telephone No.: (212) 708-1915

DATE ASSIGNMENT (DOCUMENT) EXECUTED (37 CFR 3.31(a)(7))

7. The attached assignment (document) was executed on November 30, 1995
(date)

LANGUAGE OF ASSIGNMENT (DOCUMENT) TO BE RECORDED

NOTE: "The Office will accept and record non-English language documents only if accompanied by a verified English translation signed by the individual making the translation." 37 CFR 3.26.

8. The attached document:

- [x] is in the English language.
- [ ] is not in the English language and a verified English translation signed by the individual making the translation is attached.

ORIGINAL DOCUMENT OR TRUE COPY SUBMITTED

NOTE: "Either the original document or a true copy of the original document may be submitted for recording. Only one side of each page shall be used. The paper used should be flexible, strong, white, non-shiny, durable, and preferably no larger than 21.6 x 33.1 cm. (8 1/2 x 14 inches) with a 2.5 cm. (one-inch) margin on all sides." 37 CFR 3.24.

9. Submitted herewith is:

☒ the original document.

☐ a true copy of the original document.

NOTE: "If the original [assignment] document is two-sided or the wrong size, the practitioner can comply with the requirement [set out in 37 C.F.R. § 3.24] by providing a true copy of the original document using only one side of each page on the correct size paper." Notice of June 24, 1992, 1140 O.G. 63-76, at 67.

ASSIGNMENT (DOCUMENT) TO RECORD CHANGE OF ADDRESS

(check item, if applicable)

10. ☐ Because the purpose of the attached documents is to record a change of address of the assignee, the particulars of the previously recorded assignments for each application and/or patent are shown.

ASSIGNMENT (DOCUMENT) TO RECORD CHANGE OF NAME

(check item, if applicable)

11 ☐ Because the purpose of the attached documents is to record a change of name of the assignee, the particulars of the previously recorded assignments for each application and/or patent are shown.

CHANGE OF PATENT MAINTENANCE FEE ADDRESS

(check item, if applicable)

12. ☐ A change of address to which correspondence is to be sent regarding patent maintenance fees is being sent to the Office separately.

STATEMENT (37 CFR 3.31(a)(9)) AND SIGNATURE (37 CFR 3.31(a)(10))

13. To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

NOTE: "The term 'party' as used in this rule [§ 3.31] means the person whose name appears on the documents to be recorded, that person's attorney or registered agent, or a corporate officer where a corporation's name appears on the document." Notice of June 24, 1992, 1140 O.G. 65-76, at 65.

Date: February 8, 1996

John Richards
Name of party submitting document

Signature of party submitting document

(complete the following, if the party submitting the document is applicant's attorney)

SIGNATURE OF ATTORNEY

Reg. No.

JOHN RICHARDS
c/o LADAS & PARRY
(type or print name 26 WEST 61st STREET
NEW YORK, N.Y. 10023
Reg. No. 31053 (212) 708-1915

Tel. No. ( )

P.O. Address

TOTAL NUMBER OF PAGES BEING SUBMITTED

14. The total number of pages being submitted, including cover sheet attachment(s), and documents are:

9

Total number of pages submitted

Attorney's Docket No. _____ **PATENT**

For: ☒ U.S. and/or ☐ Foreign Rights
For: ☒ U.S. Application: or ☐ U.S. Patent
For: ☐ PCT Application:
By: ☐ Inventor(s) or ☐ Present Owner

ASSIGNMENT OF INVENTION

In consideration of the payment by ASSIGNEE to ASSIGNOR of the sum of One Dollar ($1.00), the receipt of which is hereby acknowledged, and for other good and valuable consideration,

ASSIGNOR:
(inventor(s) or person(s) or entity(ies) who own the invention)

INTELLIGEN CORPORATION
(type or print name(s) of ASSIGNOR(S))
P.O. BOX 157
(Address)
COLD SPRING HARBOR, N.Y. 11724

USA
(Nationality)

If assignment is by person or entity to whom invention was previously assigned and this was recorded in PTO, add the following:

Recorded on _____
Reel _____
Frame _____

hereby sells, assigns and transfers to

ASSIGNEE:

SYNAPTECH INC.
(type or print name(s) of ASSIGNEE)
C/O SCHWARTZ & SALOMON - 42nd FL.
225 BROADWAY
(Address)
NEW YORK, N.Y. 10007-3001

USA
(Nationality)

and the successors, assigns and legal representatives of the ASSIGNEE

(complete one of the following)

☒ the entire right, title and interest

☐ an undivided _____ percent (_____%) interest

for the United States and its territorial possessions

(check the following box if foreign rights are also to be assigned)

☐ and in all foreign countries, including all rights to claim priority,

in and to any and all improvements which are disclosed in the invention entitled:

METHOD OF TREATING ALZHEIMER'S DISEASE

(check and complete (a), (b), (c) or (d))

and which is found in

(a) ☐ U.S. patent application executed on even date herewith

(b) ☐ U.S. patent application executed on _____

☐ To comply with 37 CFR 3.21 for recordal of this assignment, I, an ASSIGNOR signing below, hereby authorize and request my attorney, as named in the Declaration and Power of Attorney I executed for this invention on the execution date stated above, to insert below the filing date and application number when it becomes known.

(c) ☒ U.S. application serial no. 0 / 819,141 filed on January 15, 1986

(d) ☐ International application no. PCT/_____/_____

(e) ☒ U.S. patent no. 4,663,318 issued May 5, 1987

☐ A change of address to which correspondence is to be sent regarding patent maintenance fees is being sent separately.

(also check (a) if foreign application(s) is also being assigned)

(a) ☐ and any legal equivalent thereof in a foreign country, including the right to claim priority

and, in and to, all Letters Patent to be obtained for said invention by the above application or any continuation, division, renewal, or substitute thereof, and as to letters patent any reissue or re-examination thereof

ASSIGNOR hereby covenants that no assignment, sale, agreement or encumbrance has been or will be made or entered into which would conflict with this assignment.

ASSIGNOR further covenants that ASSIGNEE will, upon its request, be provided promptly with all pertinent facts and documents relating to said invention and said Letters Patent and legal equivalents as may be known and accessible to ASSIGNOR and will testify as to the same in any interference, litigation or proceeding related thereto and will promptly execute and deliver to ASSIGNEE or its legal representatives any and all papers, instruments or affidavits required to apply for, obtain, maintain, issue and enforce said application, said invention and said Letters Patent and said equivalents thereof which may be necessary or desirable to carry out the purposes thereof.

IN WITNESS WHEREOF, I/We have hereunto set hand and seal this

30th day of November 1995 (Date of signing).

WARNING: Date of signing must be the same as the date of execution of the application if form is not attached above.

Bonnie Davis

Signature of ASSIGNOR

If ASSIGNOR is a legal entity complete the following information

Bonnie M. Davis MD

Type or print the name of the above person authorized to sign on behalf of ASSIGNOR

Chief Executive Officer

Title

NOTE: No witnessing, notarization or legalization is necessary. If the assignment is notarized or legalized then it will only be given legal presumption of execution 35 USC 261. Use next page if notarization is required.

☐ Notarization or Legalization Page Added.

April 19, 2001

RECEIVED
MAY 02 2001
OFFICE OF PETITIONS

Dr. Bonnie Davis
Scientific Director
Synaptech Inc.
c/o Schwartz and Salomon
225 Broadway
42nd Floor
New York, N.Y. 10007-3001

Dear Dr. Davis:

Janssen Research Foundation (JRF), a division of Janssen Pharmaceutica, Inc. which is a wholly owned subsidiary of Johnson & Johnson, hereby grants Synaptech Inc. the authority to rely upon the activities of JRF before the Regulatory Authority regarding the application for extension of patent term for U.S. patent 4,663,318 ("REMINYL").

Sincerely,

Cee A. LaPree (FOR GR)

Gaetan Rouleau
Senior Director, Regulatory Affairs

ET 712821251 7 US

administer galanthamine in conjunction with another drug such as propanthelinbromide to control such arrythmias.

I claim:

1. A method of treating Alzheimer's disease and related dementias which comprises administering to a patient suffering from such a disease a therapeutically effective amount of galanthamine or a pharmaceutically-acceptable acid addition salt thereof.

2. A method according to claim 1, wherein the administration is parenteral at a daily dosage of 5–1,000 mg of galanthamine or a pharmaceutically-acceptable acid addition salt thereof.

3. A method according to claim 2, wherein said dosage rate is 50–300 mg per day.

4. A method according to claim 1, wherein said administration is oral and is in the range 10–2000 mg per day.

5. A method according to claim 4, wherein said dosage rate of 100–600 mg per day.

6. A method according to claim 1, wherein galanthamine is administered at a dosage rate of 0.1 to 4 mg/kg body weight of a patient, parenterally.

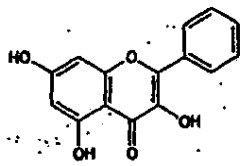
7. A method according to claim 1, wherein galanthamine is administered intracerebroventricularly via an implanted reservoir at a dosage rate of 0.01 to 5.0 mg/kg day.

* * * * *

THE MERCK INDEX

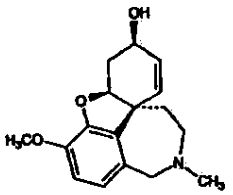
TWELFTH EDITION

Chavan, R. Robinson, *ibid.* 1933, 368. Mutagenicity studies: J. T. MacGregor, L. Jurd, *Mutat. Res.* 54, 297 (1978); J. P. Brown, P. S. Dietrich, *ibid.* 66, 223 (1979).



Yellowish needles from ethanol, mp 214-215°. Moderately sol in ethanol, ether; insol in water. Very sol in chloroform, benzene.

4357. Galanthamine. *4a,5,9,10,11,12-Hexahydro-3-methoxy-11-methyl-6H-benzofuro[3a,3,2-ef][2]benzazepin-6-ol;* galantamine; lycoremine; Jilkon. $C_{17}H_{21}NO_3$; mol wt 287.36. C 71.06%, H 7.37%, N 4.87%, O 16.70%. From Caucasian snowdrops, *Galanthus woronowii* Vel., *Amaryllidaceae:* N. F. Proskurnina, A. P. Yakovleva, *J. Gen. Chem.* 22, 1899 (1952); from *Narcissus* spp: Boit *et al., Ber.* 90, 725, 2197 (1957). Structure work: Kobayashi *et al., Chem. & Ind. (London)* 1956, 177. Synthesis and stereochemistry: Barton, Kirby, *Proc. Chem. Soc.* 1960, 392; *J. Chem. Soc.* 1962, 806; Williams, Rogers, *Proc. Chem. Soc.* 1964, 357. Alternate total synthesis: Kametani *et al., J. Chem. Soc. (C)* 1971, 1043. Asymmetric synthesis of (+)- and (−)-forms from L-tyrosine: K. Shimizu *et al., Heterocycles* 8, 277 (1977). Biosynthesis studies: D. H. R. Barton *et al., J. Chem. Soc.* 1963, 4545; W. Döbke, *Heterocycles* 6, 551 (1977). Pharmacokinetics: D. Mihailova, I. Yamboliev, *Pharmacology* 32, 301 (1986). Toxicology study: S. L. Friess *et al., Toxicol. Appl. Pharmacol.* 3, 347 (1961).



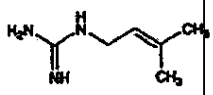
Crystals from benzene, mp 126-127°. $[\alpha]_D^{25}$ −118.8° (c = 1.378 in ethanol). Monoacidic base. Fairly sol in hot water; freely sol in alcohol, acetone, chloroform. Less sol in benzene, ether.

Hydrochloride, $C_{17}H_{21}NO_3$.HCl, crystals from water, dec 256-257°. Sparingly sol in cold, more sol in hot water. Very sparingly sol in alcohol, acetone.

Hydrobromide, $C_{17}H_{21}NO_3$.HBr, *Nivalin.* Crystals from water, dec 246-247°. $[\alpha]_D^{25}$ −93.1° (c = 0.1015 in 15 ml H_2O). LD_{50} i.v. in mice (mg/kg): 5.2 ± 0.2 (Friess).

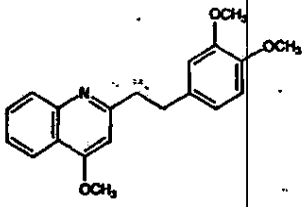
THERAP CAT: Cholinesterase inhibitor.

4358. Galegine. *(3-Methyl-2-butenyl)guanidine; N-*3,3-dimethylallylguanidine; isoamyleneguanidine. $C_6H_{13}N_3$; mol wt 127.19. C 56.66%, H 10.30%, N 33.04%. Isoprenoid guanidine deriv from seeds of *Galega officinalis* L., *Leguminosae:* Tänret, *Compt. Rend.* 158, 1182, 1426 (1914); 159, 108 (1914); Markovic, Dittertová, *Chem. Zvesti* 9, 576 (1955); *C.A.* 50, 8137d (1956). Structure: Barger, White, *Biochem. J.* 17, 827 (1923). Synthesis: Späth, Spitzy, *Ber.* 58, 2273 (1925); Babor, Jezo, *Chem. Zvesti* 8, 18 (1954); *C.A.* 49, 7495f (1955). Metabolic effects: G. Weitzel *et al., Z. Physiol. Chem.* 353, 535 (1972). Effects on mitochondria: B. Lotina *et al., Arch. Biochem. Biophys.* 159, 520 (1973). Biosynthetic study: J. Steiniger, G. Reuter, *Biochem. Physiol. Pflanz.* 166, 275 (1974). *Review:* Braun, *J. Chem. Ed.* 8, 2175 (1931).



Hygroscopic, bitter crystals. mp 60-65°. Freely sol in water or alcohol, slightly in ether. *Keep well closed.*

4359. Galipine. *2-[2-(3,4-Dimethoxyphenyl)ethyl]-4-methoxyquinoline.* $C_{20}H_{21}NO_3$; mol wt 323.39. C 74.28%, H 6.55%, N 4.33%, O 14.84%. From Angostura bark: *(Cusparia trifoliata* Engl., *Rutaceae):* Körner, Böhringer, *Gazz. Chim. Ital.* 13, 363 (1883); Tröger, Kroseberg, *Arch. Pharm.* 250, 494 (1912). Synthesis: Späth, Eberstaller, *Ber.* 57, 1687 (1924); Späth, Pikl, *Ber.* 62, 2244 (1929); Schläger, Leeb, *Monatsh.* 81, 714 (1950).

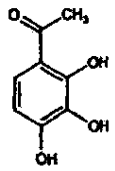


Prismatic needles from alc, mp 116°. Soluble in alcohol, benzene, chloroform, ether; slightly sol in water, petr ether. The salts are more sol than those of cusparine.

Hydrochloride tetrahydrate, $C_{20}H_{21}NO_3$.HCl.4H_2O, plates, become anhydr at 100°, mp 165°.

Methiodide, $C_{20}H_{21}NO_3.CH_3I$, yellow needles, mp 146°.

4360. Gallacetophenone. *1-(2,3,4-Trihydroxyphenyl)ethanone; 2',3',4'-trihydroxyacetophenone;* Alizarine yellow C; C.I. 57000. $C_8H_8O_4$; mol wt 168.15. C 57.14%, H 4.80%, O 38.06%. Prepn: Hart, Woodruff, *J. Am. Chem. Soc.* 58, 1957 (1936); Campbell, Coppinger, U.S. pat. 2,686,123 (1954 to U.S. Secy. Agr.); Knowles, U.S. pat. 2,763,691 (1956 to Kodak); Price, Israelstam *J. Org. Chem.* 29, 2800 (1964).



White to brownish-gray, cryst powder, mp 173°. UV (methanol): 237, 296 nm (ε 8560, 12,500). Sol in 600 p cold water, more in hot water; sol in alcohol, ether, sodium acetate.

USE: Antiseptic.

4361. Gallamine Triethiodide. *2,2',2''-[1,2,3-Benzenetriyltris(oxy)]tris[N,N,N-triethylethanaminium] triiodide; [v-phenenyltris(oxyethylene)]tris[triethylammonium iodide];* 1,2,3-tris(2-triethylammonium ethoxy)benzene triiodide; 1,2,3-tris(2-diethylaminoethoxy)benzene tris(eth iodide); tri(β-diethylaminoethoxy)-1,2,3-benzene trio ethylate; pyrogallol 1,2,3-(diethylaminoethyl ether) tri yl iodide); benzcurine iodide; RP-3697; F-2559; Tri Retensin; Relaxan; Flaxedil. $C_{30}H_{60}I_3N_3O_3$; mol wt 8 C 40.42%, H 6.78%, I 42.70%, N 4.71%, O 5.38%. Cur ing properties: D. Bovet *et al., Compt. Rend.* 22 (1947); F. Depierre, *ibid.* 956. Prepn: E. Fourne pat. 2,544,076 (1951 to Rhone-Poulenc). Comparative cal pharmacokinetics: W. Buzello, S. Agoston, *Ar* 27, 313 (1978). Mode of action: D. Colquhou Sheridan, *Brit. J. Pharmacol.* 66, 78 (1979); *elden Roy. Soc. London, Ser. B* 211, 181 (1981). Effects in malian and amphibian nerve fibers: K. J. Smith Schauf, *Science* 212, 1170 (1981).

administer galanthamine in conjunction with another drug such as propanthelinbromide to control such arrythmias.

I claim:

1. A method of treating Alzheimer's disease and related dementias which comprises administering to a patient suffering from such a disease a therapeutically effective amount of galanthamine or a pharmaceutically-acceptable acid addition salt thereof.

2. A method according to claim 1, wherein the administration is parenteral at a daily dosage of 5–1,000 mg of galanthamine or a pharmaceutically-acceptable acid addition salt thereof.

3. A method according to claim 2, wherein said dosage rate is 50–300 mg per day.

4. A method according to claim 1, wherein said administration is oral and is in the range 10–2000 mg per day.

5. A method according to claim 4, wherein said dosage rate of 100–600 mg per day.

6. A method according to claim 1, wherein galanthamine is administered at a dosage rate of 0.1 to 4 mg/kg body weight of a patient, parenterally.

7. A method according to claim 1, wherein galanthamine is administered intracerebroventricularly via an implanted reservoir at a dosage rate of 0.01 to 5.0 mg/kg day.

* * * * *

United States Patent [19]
Davis

[11] **Patent Number: 4,663,318**
[45] **Date of Patent: May 5, 1987**

[54] **METHOD OF TREATING ALZHEIMER'S DISEASE**

[76] Inventor: Bonnie Davis, 17 Seacrest Dr., Huntington, N.Y. 11743

[21] Appl. No.: 819,141

[22] Filed: Jan. 15, 1986

[51] Int. Cl.⁴ A61K 31/55
[52] U.S. Cl. 514/215
[58] Field of Search 514/215

[56] References Cited

PUBLICATIONS

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Kendall et al., J. Chem. & Hospital Pharmacol., (1985) 10–327–330.
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Primary Examiner—Stanley J. Friedman
Attorney, Agent, or Firm—Ladas & Parry

[57] ABSTRACT

Alzheimer's disease may be treated with galanthamine.

7 Claims, No Drawings

METHOD OF TREATING ALZHEIMER'S DISEASE

GENERAL FIELD OF THE INVENTION

The present invention relates to a novel method of treating Alzheimer's disease and more particularly to a treatment using galanthamine.

BACKGROUND ART

Galanthamine and acid addition salts thereof have, for many years, been known to have anticholinesterase properties. Cozanitis in Anaesthesia 29 163-8 (1974) describes the effect of galanthamine hydrobromide on plasma cortisol of patients receiving relaxant anaesthesia and Cozanitis et al in Acta Anesth. Scand. 24:166-168 (1980) describe the effect of galanthamine on plasma ACTH values during anaethesia. These studies showed an increase in both plasma cortisol and plasma ACTH when galanthamine was administered to patients together with atropine.

Il'yuchenok et al (Chemical Abstracts 70 36296K describe the appearance of θ-rhythm on an electroencephalogram when galanthamine is administered intravenously to rabbits.

Increase in short-term memory in dogs by use of galanthamine is described by Krauz in Chemical Abstracts 81 72615Z.

The antagonistic effect of galanthamine to scopolamine-induced amnesia in rats is described by Chaplygina et al in Chemical Abstracts 86 115157Z, and in Zhurnal Vysshei Nervnoi Deiatelnosti imeni P. Pavlova (MOSKVA) 26:1091-1093, 1976.

Alzheimer's disease, presenile dementia, causes much distress not only to those suffering from the disease, but also those who are close to them. The custodial care of advanced victims of the disease is a tremendous expense to society. At present, there is no effective means of improving the functional status of persons with the disease.

It is an object of the present invention to improve the cognitive function of patients with Alzheimer's disease.

SUMMARY OF THE INVENTION

A method for treating Alzheimer's disease and related dementias which comprises administering to mammals, including humans, an effective Alzheimer's disease cognitively-enhancing amount of galanthamine or a pharmaceutically-acceptable acid addition salt thereof. A radioactively-labelled form of the molecule may also serve as a diagnostic test for Alzheimer's disease.

DETAILED DESCRIPTION OF THE INVENTION

Galanthamine can be administered in any convenient chemical or physcial form. For example, it may be administered as its hydrobromide, hydrochloride, methylsulfate or methiodide.

Galanthamine or its pharmaceutically-acceptable acid addition salts may be administered to a patient suffering from Alzheimer's disease orally or by subcutaneous or intravenous, injection, or intracerebroventricularly by means of an implanted reservoir. It may be necessary to begin at lower doses than are ultimately effective.

Galanthamine and its acid addition salts form crystals. They are in general only sparingly soluble in water

at room temperature and so injectible compositions are normally in the form of an aqueous suspension. If necessary, pharmaceutically-acceptable suspension aids may be employed. Typically, such a suspension will be employed at a concentration of 1-50 mg/ml more commonly 5-40 mg/ml, for example, 5-30 mg/ml or 10-40 mg/ml, typically 20-30 mg/ml of galanthamine. Typical dosage rates when administering galanthamine by injection are in the range 5-1,000 mg per day depending upon the patient. For example, divided doses in the range 0.5-5 mg/kg body weight per day may prove useful. Typically, one might administer a dosage of 50-300 mg per day to a patient of a body weight of 40-100 kg, although in appropriate cases such dosages may prove useful for patients having a body weight outside this range. In other cases, dosages as low as 10 mg and as high as 500 mg may be appropriate for persons in this body weight range.

Galanthamine or its pharmaceutically-acceptable acid addition salts may also be administered orally, for example, as an aqueous suspension or a solution in aqueous ethanol or as a solid such as a tablet or capsule. Suspensions or solutions for oral administration are typically of about the same concentration as those used for injections. However, it may be desirable when administering the drug orally to use a higher dosage rate than when administering it by injection. For example, dosages up to 2000 mg per day may be used, such as dosages in the range 100-600 mg per day. In preparing such tablets or capsules, standard tablet or capsulemaking techniques may be employed. The dosage rate of galanthamine or its pharmaceutically-acceptable salt will normally be in the same range as for oral administration of a liquid. If desired, a pharmaceutically-acceptable carrier such as starch or lactose may be used in preparing galanthamine tablets. Capsules may be prepared using soft galatine as the encapsulating agent. If desired, such capsules may be in the form of sustained release capsules wherein the main capsule contains microcapsules of galanthamine which release the contents over a period of several hours thereby maintaining a constant level of galanthamine in the patient's blood stream.

The following test provides a good animal model for Alzheimer's disease in humans: A selective lesion is placed in a subcortical nucleus (nucleus basalis of Meynert) with a resultant cortical cholinergic deficiency, similar in magnitude to that seen in early to moderate stage Alzheimer's disease. Numerous behavioral deficits, including the inability to learn and retain new information, characterizes this lesion. Drugs that can normalize these abnormalities would have a reasonable expectation of efficacyin Alzheimer's disease. Haroutunian, V, Kanof P, Davis, KL: Pharmacological alleviations of cholinergic-lesion-induced memory defects in rats. Life Sciences 37:945-952, 1985.

The following specific formulations may find use in treatment of Alzheimer's disease:

Tablets or capsules containing 5, 10 and 25 mg galanthamine hydrobromide to be taken four times a day, or a sustained-release preparation delivering an equivalent daily dose.

Parenteral solution containing 5 mg/ml.

Liquid formulation for oral administration available in 5 mg/5 ml and 25 mg/5 ml concentration.

There have been reports that galanthamine can cause cardiac arrythmias. In such cases, it may be desirable to

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ITM NBR	PATENT NUMBER	FEE CDE	FEE AMOUNT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	4,663,318	273	245	----	06/819,141	05/05/87	01/15/86	04	YES	PAID
2	4,385,073	171	495	----	06/362,234	05/24/83	03/26/82	08	NO	PAID
3	4,666,940	173	490	----	06/767,476	05/19/87	08/20/85	04	NO	PAID

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ITM NBR	ATTY DKT NUMBER
1	U 5631
2	IFF-2741
3	U 5517

ETL 7 28 21 25 17 US

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ITM IR	PATENT NUMBER	FEE CDE	FEE AMOUNT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
	4,663,318	185	3160	----	06/819,141	05/05/87	01/15/86	12	NO	PAID

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EL 728212517 US

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David T. Read
Acting Director Health Assessment Policy Staff, CDER
Food and Drug Administration
1451 Rockville Pike, HFD-7
Rockville, MD 20852

Dear Mr. Read:

The attached application for patent term extension of U.S. Patent No.4,663,318 was filed on April 24, 2001, under 35 U.S.C. § 156.

The assistance of your Office is requested in confirming that the product identified in the application, REMINYL® (galantamine hydrobromide), has been subject to a regulatory review period within the meaning of 35 U.S.C. § 156(g) before its first commercial marketing or use and that the application for patent term extension was filed within the sixty-day period after the product was approved. Since a determination has not been made whether the patent in question claims a product which has been subject to the Federal Food, Drug and Cosmetic Act, this communication is NOT to be considered as notice which may be made in the future pursuant to 35 U.S.C. § 156(d)(2)(A).

Our review of the application to date indicates that the subject patent would be eligible for extension of the patent term under 35 U.S.C. § 156.

Inquiries regarding this communication should be directed to the undersigned at (703) 306-3159 (telephone) or (703)308-6916 (facsimile).

Karin Tyson
Senior Legal Advisor
Office of Patent Legal Administration
Office of the Deputy Commissioner
for Patent Examination Policy

cc: John Richards, Esq.
Ladas & Parry
26 West 61st Street
New York, NY 10023

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John Richards, Esq.
Ladas & Parry
26 West 61st Street

In Re: Patent Term Extension
Application for
U.S. Patent No. 4,663,318

NOTICE OF INFORMALITIES

The above-identified application for patent term extension is considered informal because the application papers do not comply with 37 CFR 1.52(a)(1)(ii) (some of the papers are on legal paper, a size not permitted by the rules of practice) or 37 CFR 1.52(a)(1) (the papers of the application are on different size paper, the rules of practice require a single size).

Applicant is required to submit two copies of the application on either 8 1/2 by 11 or A4 paper, as required by 37 CFR 1.52(a).

Applicant has **TWO MONTHS** from the date of this letter in order to file a the replacement copies. The replacement copies should be mailed to the mailing address below.

Extensions of time under 37 CFR 1.136 are **NOT** available. Failure to respond will result in the application for patent term extension being processed as an informal application. Alternatively, applicant may have the holding of informality reviewed as set forth in 37 CFR 1.740(c).

Any correspondence from applicant with respect to this matter should be addressed as follows:

By mail: Commissioner for Patents
Box Patent Ext.
Washington, D.C. 20231

By FAX: (703) 872-9411
Attn: Karin Tyson

Telephone inquiries related to this notice should be directed to the undersigned at (703) 306-3159. E-mail inquiries may be directed to karin.tyson@uspto.gov.

Karin Tyson
Senior Legal Advisor
Office of Patent Legal Administration
Office of the Deputy Commissioner
for Patent Examination Policy

cc: David T. Read
Acting Director Health Assessment Policy Staff, CDER
Food and Drug Administration
1451 Rockville Pike, HFD-7
Rockville, MD 20852

RE: REMINYL

#15

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

OCT 2 2001

Re: Reminyl
Docket No. 01E-0364

The Honorable Q. Todd Dickinson
Director of U.S. Patent and Trademark Office
Commissioner for Patents
Box Pat. Ext.
Washington, D.C. 20231

Dear Director Dickinson:

This is in regard to the application for patent term extension for U.S. Patent No. 4,663,318 filed by Janssen Research Foundation under 35 U.S.C. § 156. The human drug product claimed by the patent is Reminyl (galatamine hydrobromide), which was assigned new drug application (NDA) No. 21-169.

A review of the Food and Drug Administration's official records indicates that this product was subject to a regulatory review period before its commercial marketing or use, as required under 35 U.S.C. § 156(a)(4). Our records also indicate that it represents the first permitted commercial marketing or use of the product, as defined under 35 U.S.C. § 156(f)(1), and interpreted by the courts in *Glaxo Operations UK Ltd. v. Quigg*, 706 F. Supp. 1224 (E.D. Va. 1989), *aff'd*, 894 F. 2d 392 (Fed. Cir. 1990).

The NDA was approved on February 28, 2001, which makes the submission of the patent term extension application on April 24, 2001, timely within the meaning of 35 U.S.C. § 156(d)(1).

Should you conclude that the subject patent is eligible for patent term extension, please advise us accordingly. As required by 35 U.S.C. § 156(d)(2)(A) we will then determine the applicable regulatory review period, publish the determination in the *Federal Register*, and notify you of our determination.

Please let me know if we can be of further assistance.

Sincerely yours,

Jane A. Axelrad

Jane A. Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research

cc: John Richards, Esq.
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